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ABSTRACT

"Science as a Way of Knowing" is a project of the Education Committee of the American Society of Zoologists and ten other organizations. The goal of the project is to offer suggestions for making the teaching of biology at the college and university level more effective. The proceedings of the 1985 symposium on genetics are presented in this document. Papers included are: "Thinking and Deciding" (John A. Moore); "Science as a Way of Knowing--Genetics" (John A. Moore); "Experiments in a Monastery Garden ("Gregor Mendel," presented by Richard M. Eakin); "On the Origin of Mendelian Genetics" (Iris Sandler and Laurence Sandler); "The Structure and Organization of Genetic Material" (Monroe W. Strickberger); "The Function of the Hereditary Materials: Biological Catalyses Reflect the Cell's Evolutionary History" (Bruce M. Alberts); "Patterns of Inheritance" (Hampton L. Carson); "How Important Is Genetics for an Understanding of Evolution?" (R. C. Lewontin); "Genetics of Crop Improvement" (Michael T. Clegg); "Science as a Way of Knowing: Human Genetics" (Barton Childs); "Cultural Evolution" (Luigi L. Cavalli-Sforza); "Geneticists and Race" (William B. Provine); "Reflections on the Limits of Science and Technology" (David T. Suzuki); "Whither Mankind? The Choice between a Genetic Twilight and a Moral Twilight" (Francisco J. Ayala); "Films and Videotapes in Genetics" (Nathan H. Hart and Gary Anderson). (ML)

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SCIENCE AS A WAY OF KNOWING

An Ongoing Project of the
Committee on Education
of the
American Society of Zoologists

Cosponsored by
The American Society of Naturalists
The Society for the Study of Evolution
The Biological Sciences Curriculum Study
The American Institute of Biological Sciences
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The Society for College Science Teachers
The Genetic Society of America
and the
University of California, Riverside

SCIENCE AS A WAY OF KNOWING
III—GENETICS

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This is the third publication of the Education Committee of the American Society of Zoologists. The purpose is to offer suggestions for improving the first-year biology courses in the universities. The method consists of emphasizing the conceptual framework of the biological sciences, showing how scientific information is obtained and evaluated, pointing out the strengths and limitations of scientific procedures, and above all showing the relevance of science for human hopes and well being. This is done annually with a major symposium, an essay distributed at the symposium, a film program, and, finally, the published proceedings, which are widely distributed to scientist-teachers throughout the world. Each year a major topic is considered. In 1983 it was *Evolutionary Biology* and in 1984 it was *Human Ecology*. This year it is *Genetics*.

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III

SCIENCE AS A WAY OF KNOWING—GENETICS

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[1] James D. Watson's paper "Recollections" was given at the symposium but is not included here.
[2] A memorable impersonation by Richard M. Eakin.
[3] Paper not given at the symposium.

AMER. ZOOL., 26: (1986)

Some of the Speakers at the *Science as a Way of Knowing–Genetics* Symposium

Francisco J. Ayala (left) and William B. Provine (right)

Hampton L. Carson

Richard M. Eakin as Gregor Mendel

Monroe W. Strickberger

AMER. ZOOL., 26:573–581 (1986)

Opening Remarks: Thinking and Deciding[1]

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SYNOPSIS. Apart from providing students with the fundamental concepts and some of the data supporting these concepts, an introductory university course in biology should suggest ways of thinking about important human problems that relate to biology. Most of these problems such as abortion, genetic engineering, right to life, environmental pollution, and overuse of natural resources, have no single solution that will be accepted by all people. Science cannot specify what the solution should be—that must be a human choice. However, the data and procedures of science can be invaluable in helping human beings make informed choices and, once a choice has been made, make more probable the achieving of the desired goal.

In the City of Baltimore, the home of Johns Hopkins University, what could be more appropriate to explain what *Science as a Way of Knowing* is trying to do than to begin with a statement by Hopkins' renowned Professor of Zoology, William Keith Brooks (1882, p. v):

> Most lecturers upon natural science find, no doubt, that preliminary work, the presentation of facts upon which science is based, absorbs so much time that there is no room for a philosophical discussion of the scientific aspects of the subject.

More than a hundred years later the *Science as a Way of Knowing* project is attempting to deal with that same problem by offering suggestions for improving the first-year biology courses in colleges and universities. We have three goals: to lessen the factual load that characterizes so many classes and textbooks, to increase the attention given to the conceptual framework of biology, and to emphasize the importance of scientific information and procedures for human welfare. In attempting to achieve these goals we approach science as a way of knowing and emphasize its strengths and limitations (a more detailed description of our goals will be found in Moore, 1984, pp. 421–422 and 469–473; Moore, 1985, pp. 377–378, 486–489, and 612–615).

The reader of these *Science as a Way of Knowing* series may have difficulty in relating the lengths of our publications with our stated goal of lessening the factual load of biological information. We must emphasize, therefore, that these yearly publications are not intended as material to be presented *in toto* to students but as background information for teachers. We hope that the material will provide teachers with considerable understanding of the evidential basis for the concepts that are to be taught. As has been suggested before, a teacher must know a very great deal to be able to say properly only a very little on any single topic in an introductory course in biology. A student, on the other hand, needs to know the concepts but time will not allow a full measure of proof to be provided, even if such were desirable.

Today the teaching of science has taken on an importance that it has never had before. There was a time when the goal need be no more than explaining the natural world to an inquiring mind seeking a broad liberal education. But today science impinges so much on the life of individuals and nations that it is essential that an effective proportion of society understands its nature, strengths, and limitations. One can no longer teach genetics only as genetics but must teach genetics also as a science. The reason for this is that our nation and the world seem to be pitted against an ever-increasing galaxy of problems that relate to our interactions with one another and with the natural world. Many of these problems demand solutions, yet there is no

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[1] From the Symposium on *Science as a Way of Knowing—Genetics* presented at the Annual Meeting of the American Society of Zoologists, 27–30 December 1985, at Baltimore, Maryland.

the answer for what should be done. Whatever decisions are made depend on one's mode of thought and whether one thinks of today only or of the future as well.

Scientists have much to say about these matters. They have perfected a system of thought that is without equal for obtaining verifiable information, and scientific information is absolutely essential for balancing short-term and long-term plans for our interactions with the non-human world. Thus, I would like to say a few words on these two subjects: how we think and how we plan.

First about how we think. Creationists have taught us an important lesson which is that all human beings do not think the way scientists do. It is very important that we discuss these different modes of thought with students who often come to us believing that creationists and scientists have equally valid explanations for the origins of life and for its changes over time. That being so the students often assume that one or the other modes of thought may be selected with impunity. In many instances that can be a dangerous conclusion.

In the creationism–evolutionist controversy it is especially clear that there are two ways of explaining the same phenomena and it is important that students understand why such different conclusions can be reached. There is no need to survey for this audience the arguments between the creationists and the scientists but is important to note their very different premises. The answers to the creationists' questions are to be found in the first two chapters of *Genesis* and, no matter what they say under the rubric of "creation science," it all comes back to an intense faith in the inerrancy of the Judeo-Christian Bible. Had there been no mention of creation in the Bible it is most likely that the fundamentalists of today would be staunch evolutionists for there is no other verifiable explanation than evolution for the diversity of life on earth. Creationists have no difficulty in regarding the accounts of creation in other religions as myths, but that clarity of thought fails with their own.

Creationism begins with the answers for the origins of life and the reasons for the diversity of species, and then attempts to adjust the data of science to the already-accepted beliefs. This can be done quite readily. If one accepts the possibility of supernatural processes, anything and everything can be explained—God wants it to be that way.

But science cannot use supernatural processes either in its premises or in its conclusions. A scientist can offer explanations for the origins of life and organic diversity that employ only natural things and processes. Mutation and natural selection are natural processes that can be studied by observation and experimentation.

The basic difference, then, between creationism and evolutionary science is the source of evidence. Evidence for a special creation is based in the last analysis on the accepted beliefs, the received traditions, of the religious sect. These beliefs all involve supernatural events and processes. On the other hand, evidence for the evolution of life comes basically from the fossil record and to a lesser degree from studies of living forms. This evidence can come only from observations and experimentation involving natural things and processes.

Little of this will be news to those who teach first-year students but few students are aware of the fundamental differences between creationism and biological evolution. Many will wonder which is the better explanation. Here we have to accept that there is no *the* answer. Therefore, which explanation should be accepted? If one places the religious mode of thought above all others, the answer is to believe the particular creation myth that goes with the sect. Faith permits one to require no proof for beliefs and to be troubled neither by the creation myths of other sects or by the verdict of science. If one prefers to rely on the data of science and the verified statements of scientists, a different mode of thought is employed and a vastly different conclusion is reached.

All of us should acknowledge that a person has a right to believe anything whatsoever. But does it make any difference? Probably not if the individual limits rejection of modern science solely to the question of evolution. It does matter if all modern science is to be rejected. It is absolutely essential that a determining fraction of society understands what science is and what it can and cannot do. For some years now the human population has had severe problems in its relations to the natural world, and in many instances purely human problems also have their roots in natural processes. It is imperative, therefore, that the educational establishment teaches science effectively if these problems are to be understood and solutions sought.

Science has become the most dramatic force in the modern world. Science is power. It can be power for tremendous good or it can be power for tremendous evil. Whichever scenario is followed depends absolutely on human decisions. Science has no life of its own—it is but one aspect of what it means to be human. It must be accepted that science says only what can be done, not what should be done. That statement implies that we are dealing with two phenomena: the way science works and the way human decisions are made. Science tells us that not everything we might wish to do is possible, some things being precluded by the laws of nature. Human beings may seek to circumvent these laws but they cannot repeal them. In making decisions, however, we like to believe that the human mind is free of all fetters and that our humanity is based on that freedom. But decisions about the natural world can no longer be made so freely.

We touch here on a familiar problem—different people think in different ways, and even the same person will think differently depending on the problem requiring analysis. One oversimplifies the dichotomy of thought patterns by recognizing two dominant modes: the scientific pattern of thought *vs.* all others. C. P. Snow (1963) emphasized this in his *Two Cultures,* where he deplored the almost total isolation of the sciences and the humanities in the universities and in the world beyond.

It seems essential that these matters be dealt with in science courses. In a recent editorial the new editor of *Science,* Daniel Koshland (1985), has this to say:

> It is time to consider the problem of biconceptual education. The world is divided into two conceptual groups, the scientist and the nonscientist, and the communication gap between them is wide and serious . . . . What concerns me is that some of the fundamental concepts and methodologies of science are outside the understanding of the vast majority of the population, including the opinion makers . . . . Examples of scientific concepts are directly transferable to public policy and should be taught to students at the elementary, high school, and college levels . . . . Instead most schools today are diminishing science requirements. Even at the college level, the few universities that have general education requirements allow them to be satisfied by tourist-bus surveys of the wonders of astronomy or the marvels of the body, rather than by a more demanding course in the simple logic of science . . . . Scientists will be denounced for trying to introduce cold-blooded reason into an area in which warm-blooded humanity is supposed to reign supreme. But warm emotion frequently gives rise to hot-headed anger and even bigotry. The scientific method has been the most effective means of overcoming poverty, starvation, and disease. Even those who are not professional scientists can understand its fundamental concepts, which will aid their decision-making in an increasingly difficult and technological world. It is time to bridge the "concept gap" by improving scientific literacy . . . .

And so it is. Students should become able to deal with these matters in a substantial manner.

The scientific mode of thought must, in the final analysis, be based on events that can be studied by observation and experiment. Astronomers no longer explain the movement of the celestial bodies as reflections of divine purpose. Their observations can be explained according to the rules of physical science. Medical scientists explain disease not as consequences of divine wrath but in terms of biology and biochemistry.

This scientific mode of thought is not restricted to the sciences. A detective assembles the clues (data) to a murder, develops a hypothesis to explain the crime, and then tests this hypothesis in various ways: "Where was the suspect at the time of the crime?" An automobile mechanic uses similar scientific procedures in determining that the automobile will not run—because the battery is dead.

Consider the fundamentally different mode of thought of those in the legal profession. Their ultimate point of reference is the law of the land. Laws are based on what human beings have decided is necessary for the health of society. They began as rules to regulate human behavior and sought little or no control over the interactions of human beings with the environment.

And, as we have seen, the religious mode of thought is based on belief in a deity or deities and what the deities wish us to do. We enter here the realm of supernatural phenomena where statements cannot be tested for their validity and accepting them is a matter of faith.

It is most important that we realize that there are these different modes of thought, each with its strengths and limitations. We can ignore intermediate links and positions and note the main characteristics of each and oversimplify by saying that:

Science deals with what is in nature; the humanities deal with the products of the human mind (for convenience we exclude science itself, which of course is a product of the human mind). Or we might say, science turns out to nature and the humanities turn inward to self.

More specifically we see this dichotomy also when we compare what artists and scientists do. At the onset of their enterprises, artists create and scientists discover. That is, the artist is expressing some vision that arises from within. On the other hand, the scientist discovers natural phenomena, then tries to relate them one to another, and finally to express these relationships as conceptual schemes. These natural phenomena exist whether or not there are scientists seeking to discover them—the stars ran their courses before there were astronomers—or even other human beings. The scientist may exhibit great creativity in the way observations are made and experiments designed and in the formulation of the conceptual schemes after the discovery stage has been passed. Michelangelo may have thought that he was only liberating *David* from that block of marble, but we may suspect that there would not have been that *David* had there been no Michelangelo. More likely that block of marble would have ended as a wall or as cement.

In the sciences there is often a single answer to a question, that is, a specific cause usually has a specific effect; in the humanities there may be many answers.

In the sciences one deals with the phenomena of nature, attempts to reduce them to conceptual schemes, and tests these conceptual schemes against the phenomena of nature itself. Nature is the final arbiter. In the humanities one deals with opinion, emotion and, in the case of religion, with supernatural phenomena and received traditions. Human choice is the final arbiter.

Science is constrained by the laws of nature; the humanities express the freedom of the human spirit.

Science deals with the correct and incorrect; the humanities may deal with good and evil, beauty and ugliness.

Science is (should be) value free; the humanities may deal with value.

Most of us will have problems with these statements but they are intended only to suggest the distinctiveness of the two main modes of thought and action that are thoroughly intertwined in the decisions we make in everyday life. These decisions nearly always have a large fraction of humanistic thought and a modicum of scientific analysis. This is inevitable—the humanities are what human beings are all about. Nevertheless, in the world today, it is abundantly clear that human hopes and aspirations are dependent on science for their fulfillment. It is therefore important that we explore what science has to offer in solving human problems.

So how can we reform the teaching of science in such a way that our students, the decision makers of tomorrow, will learn to use its procedures and data to better solve those problems that have no simple answer or single solution? There are valid reasons for the almost universal requirement that students must have completed some work in science before they are allowed to graduate. Since science has become such a spectacular and dominant element of civilization there is acceptance that all educated persons must be familiar to some degree with its nature and processes. They must be familiar with some of the important conclusions of science as well as with the processes that led to these conclusions. These are some of the features of science that are judged worthy of study and, at times, of imitation.

1. Scientific research is a highly disciplined enterprise. Data must be collected with great care, often with expensive equipment, and checked repeatedly. The data of science can come only from observations and experiments of natural phenomena and they must become part of the general statements or of the conceptual schemes of science.

2. The conceptual scheme itself must be tested, not only by the original investigator but by other competent scientists, until the statements can be accepted as true beyond all reasonable doubt. The body of scientific knowledge, therefore, becomes the responsibility of all scientists. The Theory of Evolution has been tested, modified, extended and in fact is the product of a large group of scientists. In the humanities it is different—only W. Shakespeare created and is responsible for *Hamlet.*

3. The repeated testing and additions of new data make science a progressive enterprise. In any active field of science, the science of today is superior to the science of yesterday.

4. Nature is not all chaos and its phenomena are being reduced to rational conceptual schemes. Once these conceptual schemes have been formulated, they remain reliable predictors of future phenomena.

5. Ideally there is a free exchange of ideas among scientists throughout the world. There is no American Chemistry, French Biology, Russian Mathematics, or, with apologies to Nicolaus Copernicus, no Polish Astronomy.

6. So we should convey to students the notion that science as a way of knowing can be disciplined, reliable, confirmable, international, inspiring and, I might add, a source of great intellectual satisfaction.

7. But more than anything else we must convey to students that the human population is utterly dependent on the natural world; that today we are abusing that world to a degree that compromises a human, and certainly a humane, future; that we must begin to pay far more attention to our interactions with the natural world; that we must begin to make some very difficult decisions about these interactions; that scientific information can assist us in making these decisions, and that once the decisions have been made scientific procedures can help us reach the desired goals.

8. And we must encourage students to think of both the short-term and long-term consequences of their decisions.

Items 7 and 8, just listed, are of such critical importance in science education that I will offer examples of how they might be explored with students. There are many topics in genetics that could be so treated such as abortion, amniocentesis, or genetic engineering.

Take, for example, Alzheimer's disease, a tragic and destructive concomitant of the aging process in as many as two million Americans—a percentage that will increase as life expectancy increases. There is no known cure. Let us assume (the data are not in) both that the disease has a genetic basis and that within a decade it will be possible to detect the gene(s) in amniotic cells. Consider the case of a couple with some family members having Alzheimer's disease. The couple is expecting a baby and amniocentesis shows that the baby has the genes for the disease. What should the parents decide? Should there be no intervention? In this case the child would, in all probability, lead a normal early life. Nevertheless, the child could expect a tragic old age. The parents would live with that knowledge whether or not they informed the child. Should the child have children, when mature, and increase the tragedy for the next generation? Should the parents "let nature take its course" hoping that a cure might be available before their offspring reaches late maturity? Or should the parents agree to an abortion and try again—hoping for a normal baby? There is no answer to this problem but it is possible for a biology teacher to present the available data and suggest the probable outcome of various choices.

In undertaking to discuss problems of this sort with students, it may be wise to begin with an example less involved with human emotions and for which the "right" answer may appear to be more obvious, at least to idealistic students. Acid rain or, more properly, acid deposition is an example of what might be a better first choice.

Acid deposition is a source of concern not only for those in the Northeast but, increasingly, of many other parts of the United States, Canada, and Western Europe. Lakes and forests are dying and agricultural productivity is diminishing. A century ago it would have been impossible to determine the reason but the sophisticated procedures of science allow us to identify the cause—the oxides of nitrogen and sulfur that are produced by the combustion of fossil fuels in automobiles, factories, and power plants.

Acid deposition would be of little consequence in the Northeast if it were derived only from the oxides of sulfur and nitrogen produced locally. But to this small local production there is added a very large amount of pollutants that are carried by the winds from the area between the Alleghenies and the Mississippi River to the Northeast. This same source adds to locally produced pollutants in Canada that are causing severe damage there.

It is interesting to observe that the problem of pollution in New England was caused by a partial solution of the problem of pollution in the Central States. It has been known for a long time that the toxic fumes of industry have a deleterious effect on plants, buildings, and human lungs. So in an effort to reduce this problem engineers built exceedingly tall smoke stacks. These carry the pollutants high into the atmosphere where they are transported long distances—on the average the pollutants will not settle to the earth until they have traveled 500 to 1,000 kilometers. Thus, instead of being deposited on the people, homes, and vegetation where they are produced, the pollutants supposedly would be effectively diluted by being spread over a wide area.

It must be remembered also that natural cycles can cleanse the environment—after all, the *total* amount of gases that has come out of the factory smoke stacks and the exhaust pipes of our automobiles since 1900 is not still here for us to breathe. Rain and ordinary settling carry many of the polluting molecules to the earth where bacteria and other organisms convert them to forms that can be used in our bodies. The sulfur, nitrogen, and oxygen that produce the toxic oxides are essential substances for all life. These pollutants, with apologies to the weeds, are no more than molecules out of place.

Tall smoke stacks were a fine solution of the problem—no one really suffered—until the tremendous growth of industry after World War II added greatly to the load of pollutants spewed out of those tall smokestacks and into the atmosphere. The point was reached where the natural cycles could no longer cope with the load of pollutants. Nature was being overwhelmed with poisons.

Not only are scientists able to determine why the lakes and forests are dying but they also can provide a cure—known technology can reduce the level of pollutants to a point where they do little harm.

The answer as to what should be done will generally seem obvious to students and they find it difficult to understand why, when a serious problem can be corrected, it is not. So we must explain to students that, no matter how unsatisfactory it may be, we must accept that for many of the pressing societal problems of the day there is no consensus for *the* answer. Yet these problems demand answers and the only course of action is to choose whichever scenario we predict will produce the more favorable outcome. More often than not these decisions have been made on the basis of inspiration rather than information. With proper information the procedures of science may be of great value in making choices—but they can teach us only how to think, not what to decide. It is important that we understand that distinction.

At this point it is useful to introduce students to Garrett Hardin's (1968) classic fable, "The Tragedy of the Commons." The Commons is that of Colonial New England where the inhabitants of a village were free to graze their cows. Let us suppose that the Commons was only large enough for the ten families of the village to each put one cow out to pasture and that each cow will produce one gallon of milk per day.

Let us next suppose that one family decides to put two cows on the Commons. This they can do legally but the quantity of grass is now not quite sufficient for the 11 cows. Let us suppose that each cow now produces only 0.9 of a gallon of milk. Nine of the families would suffer somewhat—they would have only 0.9 of a gallon per day. The family with two cows would have 1.8 gallons. Seeing what is happening, another family decides to protect its "rights" by also having two cows. Each cow now finds only food for 0.8 of a gallon and that is all eight of the families get. The other two families, however, each receive 1.6 gallons of milk per day.

A Tragedy of the Commons is inevitable when resources are finite (as they always are) and their exploitation is not regulated.

This metaphor of the Commons will help students understand why the problem of acid deposition is so difficult to solve. The available scientific data seem sufficient to suggest remedial actions but it is to the advantage of some to abuse the Commons, in this case the atmosphere, even when it results in a severe disadvantage to others. It is beginning to seem astonishing that we are allowing a resource absolutely required for life, air, to be severely abused. In a sense the problem is new. "Air" was assumed to be so abundant and requiring no effort for us to obtain—it is "free." The legal system had been slow to regulate the use of those resources that are "free."

Thus, so long as only a limited amount of pollutants was liberated into the atmosphere there was little harm. They were diluted and the natural cycles removed them from the atmosphere. But since the size of the human population and the level of technology have grown so greatly, there is a vast increase in the burning of fossil fuels and the natural purifying cycles are overwhelmed; hence the death of lakes and forests in New England—far from the source of their executioner. A similar example occurs where I live in the Los Angeles Basin—breathing is hazardous to my health many days each year.

New England would gain if available technology were used to reduce the quantity of pollutants leaving the far-away smokestacks. But New England's gain would be a loss for the Midwest—it would be expensive to install and maintain the equipment (as a matter of fact it pays for itself in some situations). Eastern Canada is at a similar disadvantage and demands that the United States do something. The response of our government is usually no more than to plan another conference, or better, to demand more scientific data. A proposal that calls for more scientific information is an almost foolproof scenario for avoiding doing something that one really does not wish to do. How can one possibly be against more scientific information? It matters little that most experts believe that sufficient data are already in hand to solve the problem.

Thus once again we present students with a case where there is no *the* answer. There may be one answer for citizens of New England and Canada and another for the industrialists of the Midwest. One cannot turn to science to determine what must be done. What is done is a human decision that balances the short term gains for the Midwest against the long-term gains of New England. In this case, as with all involving our relations to the environment, scientific data may help us to reach a decision, but it cannot dictate one.

Nevertheless, I think it not only reasonable, but mandatory, for science teachers to help students deal with problems of this sort. Scientists have special qualifications because they are the ones who monitor our relations with the environment, who document the adverse effects of human behavior on it, who can often suggest workable solutions, and who are likely to consider the long-term consequences of different plans of action.

These environmental problems are here now, and are serious. One rarely picks up a major newspaper without being informed of problems of toxic wastes seeping into the aquifers, of poor agricultural practices ruining the soil, of contaminated food, water, and air, and of wild species of animals and plants being adversely impacted or exterminated.

We are treating much of our world as a Commons in ways that lessen its ability to support life. We are squandering our nonrenewable resources—oil, gas, coal, metals—and using renewable resources—air, water, soil, animals, and plants—at rates that exceed their ability to regenerate. Thus, it is mandatory that we educate students to a degree that they will make decisions that will lessen the probability of a worldwide and terminal Tragedy of the Commons.

A second role of a teacher is to encourage students to balance short-term and long-term gains when they are making decisions. Emphasis on short-term gains has seen the near extermination of the great whales that cruise one of the greatest Commons of all—the sea. The great whales could have been harvested at a rate that would have provided a steady supply of food and oil forever. It is only now, when commercial whaling is of greatly reduced value, that there are serious international efforts to preserve the whales. The fishing banks off New England and eastern Canada have come close to a similar fate and their future is by no means assured.

Neither the recognition of the problems of exploitation of the Commons nor of short-term and long-term gains insures that we make decisions that will preserve the ability of the environment to support human life. Something more is needed.

So here we come to the most difficult problem for students—and for us. We have to make choices and I suggest that a single age-old ethical principle will not be found offensive to the vast majority of students or to their parents: whatever we do for our own advantage should not be unacceptably harmful to others, or to the environment—either now or in the future. We have to adjust our life-styles so that we live largely on the interest, not the capital, of this planet. This means that we cannot use renewable resources at a rate greater than they are regenerated and that we must use non-renewable resources with the greatest prudence. There is simply no alternative if a human future is to be assured.

So I conclude that the time has come, in fact it is long overdue, when we must stop teaching the sciences only in their conceptual purity and we must extend them to our messy human world. That world need not be messy. We have the science and technology to make this world a fit place for human life. The problem is not what we can do as scientists but what we decide to do as human beings. We have the ability to adequately feed, clothe, and house a limited number of human beings and for them we could provide adequate medical treatment and cultural and recreational opportunities—a good life, in fact, a very good and rewarding life.

But to do these things we have to change the ways we live and breed if we are to avoid a Tragedy of the greatest Commons of all. The earth's crust cannot provide a good life for an ever-increasing number of human beings who continue to squander and destroy the natural resources that are required for life and demand social resources beyond the ability of society to supply. These matters, difficult and controversial, must direct the teaching of science.

This point of view requires that we accept the proposition that the human drama is worthy of playing well into the future and that we are willing to forego some short-term advantages to ensure that future. To be sure we have had our ignoble days but there is no doubt that the human drama represents the most astonishing fact of life on earth. It is not fashionable today to extol the human experiment but we alone among the species have the ability to control our destiny. That destiny can be, but might not be, a splendid achievement. Somehow the desires of our humane side must be moulded by the understandings that science gives us about the natural world and our relations to it.

And my final thought: We must convince our students that we cannot afford to think only as scientists or as humanists. Either we think or we do not.

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Science as a Way of Knowing—Genetics[1]

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SYNOPSIS. This essay is part of the third presentation of an educational project of the American Society of Zoologists. The purpose is to offer suggestions for improving the first-year biology courses in the universities. The method consists of emphasizing the conceptual framework of the biological sciences, showing how scientific information is obtained and evaluated, pointing out the strengths and limitations of scientific procedures, and above all showing the relevance of science for human hopes and well being. This is done annually with a major symposium, an essay distributed at the symposium, a film program, and, finally, the published proceedings, which are widely distributed to scientist-teachers throughout the world. Each year a major topic is considered. In 1983 it was *Evolutionary Biology* and in 1984 it was *Human Ecology*. This year it is *Genetics*.

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[1] From the Symposium on *Science as a Way of Knowing—Genetics* presented at the Annual Meeting of the American Society of Zoologists, 27–30 December 1985, at Baltimore, Maryland.

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INTRODUCTION

During the past year the educational establishment has passed from the stage of producing innumerable reports documenting the Decline and Fall of (precollege) Education in America—the Chicken Little Stage—to that of serious attempts at remedial actions. There are moves to increase rigor in the classrooms; a greater appreciation by students that education is a serious and difficult matter; an acceptance that the nation's welfare depends on drastic and dramatic educational reform; moves to eliminate the educational fluff that was blown in during the post-war years and to increase the competence and professionalism of the teachers, and the reluctant admission that the schools may be better at education than they are in dealing with social problems that society as a whole has been unable and often unwilling to solve.

In the many discussions and programs concerned with educational reform, the colleges and universities have generally escaped scrutiny and condemnation. This is most surprising, since it is the universities that define the fields of learning, add notably to new knowledge, and educate those who will become the teachers in the schools. Just as parents must assume responsibility for their biological children, so must the university assume responsibility for those of their educational children who will teach in the schools.

The *Science as a Way of Knowing* project *is* concerned with higher education. It seeks to offer suggestions for improving the introductory courses in biology at colleges and universities and, by extension, to other courses in biology and the sister sciences. Each year a major field of biology is considered. In 1983 it was *Evolutionary Biology*; in 1984 it was *Human Ecology*. This year's topic is *Genetics*. Tentative plans schedule *Developmental Biology* for 1986, *Form & Function* for 1987, *Cell Biology* for 1988, and *Brain & Behavior* for 1989.

Our *modus operandi* consists of organizing a symposium at the Annual Meeting of the American Society of Zoologists where outstanding scientists deal with various aspects of the topic for the year. We also provide those attending the symposium with a long essay (this being an example), present a film program and, finally, the published proceedings are distributed throughout the world.

The relationship between the papers by the symposium speakers and this essay should be noted. The greater length of the essay permits a broader treatment of the conceptual foundations of the topic being considered and the inclusion of more extensive references. The individual papers, while dealing also with broad conceptual schemes, tend to emphasize the current state of knowledge. This dichotomy will be especially noticeable this year. There is so much to cover in the vast field of genetics that the essay will deal only with the fundamental developments up to the early days of molecular genetics when one could conclude that, beyond all reasonable doubt, DNA is the primary substance of inheritance. The accompanying papers of the symposium speakers will carry the analysis to the present day.

There is one notable omission from this year's symposium—a discussion of the genetic basis of development. That topic will be postponed until next year when the topic is *Developmental Biology*.

We must emphasize, once again, that the *Science as a Way of Knowing* project intends to provide *background* materials. Every year we have presented far more material than could or should be included in an introductory course occupying a full academic year. There is a reason for this apparent surfeit. It can be argued, correctly I believe, that there is an inverse relation between what a teacher must know and the length of time that can be allowed for the development of the topic. One must know a very great deal to be able to say properly a very little. That, of course, is the main difficulty and the main challenge for those who teach first-year courses in science.

THE PARAMETERS OF OUR APPROACH

Our title, *Science as a Way of Knowing*, defines our basic approach. We emphasize the conceptual framework of the biological sciences in the belief that the introductory courses will be more effective and satisfying if they deal primarily with ideas and the data supporting these ideas and not mainly with vocabulary. We seek to show how scientific information is obtained and evaluated—something that citizens of a democracy must come to understand.

While we will be concerned almost exclusively with science as a way of knowing, we must not forget that there are other ways of knowing with great human appeal. In science we seek to understand natural phenomena using data derived from observations and experiments on those natural phenomena. Great pains are taken to exclude rigidity of thought, emotion, acceptance of *a priori* statements, personal opinions not based on scientific data, and supernatural explanations. Ideally we seek to believe only what nature tells us, not what we might wish to believe for personal, religious, political, or other reasons.

The power of the scientific way of knowing is that whatever answers are obtained must be verifiable by all other scientists with equal wisdom, skill, and open-mindedness. Thus the procedures of science are self-correcting.

This way of knowing is to be contrasted with that of philosophy, religion, and many of the humanistic disciplines where opinion often takes the place of verifiable conclusions. But having said that, we must recognize that many people prefer those answers derived from non-scientific modes of thought—as do scientists for many aspects of human life. The contrast between these two modes of thought becomes important when we ask what is the purpose of the answer being sought. Science has proved a powerful device for solving many of the problems that stem from the interactions of human beings and the nonhuman world around them and even some of the problems of the interrelations of human beings themselves. Nevertheless, we cannot look to science to tell us what is good, just, beautiful, or even enjoyable. In many instances, however, we may find that scientific information can help us predict the outcome of various human-based decisions and, once the decisions have been made, scientific procedures may help us to achieve the desired goals.

University courses in science must provide an effective understanding of the strengths and limitations of scientific procedures. The power and possibilities of science are shaping our lives and future prospects more than any other aspect of civilization. We cannot allow its control to reside with a detached elite.

There is wide acceptance that one important goal of education is to give students experience in solving problems. If this is accepted, then it is necessary to deal explicitly with problem solving and not just with solutions.

Our students, the future leaders of society, must come to understand that scientific knowledge is the *sine qua non* for developing new and necessary relationships with the natural world. Our world is no longer boundless of space and resources. We must adjust to living on the interest it provides, not the capital. We must develop this new relationship if humanity is to avoid an unparalleled and possibly terminal disaster.

But above all our students must come to accept science as a powerful device for achieving human goals while realizing that it is both inappropriate and impossible for science to define those goals. Science is an expression of what it is to be human.

In the field of education it is far easier to say what should be done than to do it. You must judge the degree to which this essay, and the symposium of which it is a part, achieve our goals. We will profit greatly from your suggestions and verdict.

A NOTE ON THE REFERENCES

Most of the references are grouped at the ends of the major sections of this essay. I have been able to check nearly all of them but, where this was not possible, there may be errors in the citations. The references are primarily those that are of interest to teachers but they range from those that would be appropriate for first-year students to the fundamental research literature. Those titles identified with an * provide excellent introductions to the topic being considered.

THE CENTRALITY OF GENETIC THEORY

In 1973 Th. Dobzhansky issued his famous challenge to the creationists, "Nothing in biology makes sense except in the light of evolution." True enough, but there is something even more fundamental from which all the other major concepts of biology are derived.

The fundamental characteristic of life is its ability to replicate almost exactly by transforming the materials and energy of the non-living world into more of itself. Genetics is the field of investigation that seeks to understand this phenomenon of replication and, hence, must be considered basic to all biology. Replication and all other aspects of life are reflections of the structure and functioning of the genetic materials—the nucleic acids. Evolutionary biology is the field that investigates the long-term aspects of replication. Developmental biology is the field of investigation dealing with those aspects of replication that occur within the lifetimes of individual organisms. Systematic biology studies the diversity of life that is a consequence of replication being modulated by the environment over time. Ecology deals with the interactions of the environment with the genetically-programmed individual and groups of individuals. Morphology and physiology are the structural and functional consequences of the activities of the genetic materials at all levels from cell to organism.

Thus, there can be no more fundamental field of biology than genetic replication. Genetics first and foremost, including its long-term manifestation—evolutionary biology—is the integrator of all biological concepts and data.

This concept of the unity of biology based on genetics may be useful if presented to students at the onset of their study of genetics but its full significance will be better appreciated if it is repeated as the course progresses.

Today there are special problems in teaching genetics to first-year students. The science is developing so spectacularly and rapidly that there is a great temptation to present mainly the latest results—when there are so many exciting things to say, it is difficult not to say them. When this is done without first providing students with the conceptual framework of the field, the "latest" may be information that can be memorized but may be impossible to understand or appreciate. What is "old" for scientists can be "new" for students. Thus, learning about sex chromosomes or how the substance of heredity was discovered to be DNA will be heroic, important, and exciting stories to those unfamiliar with how these puzzles were explicated. Or, as J. R. Baker (1955, p. 450) put it:

> In many fields of science we must recognize an embryology of ideas: our modern outlook can only be fully grasped and assessed if we understand the causes that make us think as we do.

This advice of a generation ago is even more important today. The rate of progress in fleshing out the conceptual framework of biology is so great that there is danger that with an overload of information we will forget the conceptual framework itself. Students must not be overstuffed with information and starved for understanding.

WHAT IS THE QUESTION?

Science, as a way of knowing, is a powerful device for gaining an understanding of the natural world. Some will maintain that it is the only source of a systematic, verifiable, and conceptually adequate way of obtaining such understanding. Yet understanding rarely comes from attempts to answer what appear to be the obvious questions. Thus one obtains only a superficial understanding by employing the simple procedures of random observations of natural phenomena. Instead modern science has entered a Golden Age because it seeks answers to specific questions (hypotheses), which often seem trivial and not closely related to the "big questions."

Surprising as it may seem, *one of the greatest obstacles to understanding the natural world is not knowing what questions to ask.* This point can be brought home to students by projecting a color slide of a mountain, for example, and asking those students unfamiliar with geology to suggest some of the scientific questions one might ask about that mountain. Only a genius is likely to suggest anything very profound. A professional geologist would be able to supply much information about the age, composition, and method of formation but very little of the answers could be obtained by observations on that mountain alone. Instead, understanding would have come from the synthesis of many observations and experiments in the fields of sedimentation, radioactive decay, erosion, vulcanism, chemistry, mineralogy, and plate tectonics.

This point can also be illustrated beautifully by a review of the difficulties scientists had in coming to understand what is involved in inheritance. Genetics, now the most rigorous and conceptually complete field of biology, has reached this stage only in our lifetime. For millennia human beings had no useful answers about inheritance because they were unable to formulate useful questions. In science, useful questions are those that are amenable to observation and experiment and, hence, susceptible of being answered.

Thus, for most of human history, inheritance was no more than a vague principle lacking precise rules and predictive value. Consider, for example, the sorts of data that people were likely to gather. The children of a human couple would, routinely, differ from one another in many ways. Some would be female, others male—a truly profound difference. Unless the children were identical twins, the sibs might differ strikingly in appearance and personality. At times the children would have little resemblance to the parents yet, at other times, there might be a strong familial resemblance. How could the same cause—reproduction by the same parents—lead to such diverse results?

Yet there were some regularities. The children of American Indians, Blacks, Orientals, and Caucasians were observed to have the general characteristics of their race. Until our century, observations on a variety of organisms produced no more precise answers than, only in the most general way, do offspring resemble parents. No precise rules were discovered that related the characteristics of offspring to those of the parents. Those vague answers were all that could be expected from the vague question, "What is the nature of inheritance?" There was no acceptable way to account for the observation that inheritance seemed to consist of the transmission of similarities, differences, and even novelty.

Since the educational value of science lies not only in the information that it provides but also in the manner of obtaining that information, there is value in exploring past attempts to understand the nature of inheritance. As with so many topics in biology, it is convenient to begin with the Greek philosophers. Not infrequently they defined the problem and suggested the main hypotheses that lasted into modern times. We will consider only two: Hippocrates and Aristotle.

HIPPOCRATES

Hippocrates, usually recognized as the Father of Medicine, might also be accepted as one of the Fathers of Genetics. Writing about 410 B.C., he proposed *pangenesis* as an explanatory hypothesis for inheritance. Pangenesis assumes that inheritance is based on the production of specific particles ("seeds") by all parts of the body and on the transmission of these particles to the offspring at the time of conception. Darwin was to adopt a similar explanatory hypothesis long afterwards and pangenesis was to remain the only general theory of inheritance until the end of the 19th century.

One of the observations that led Hippocrates to this belief concerned a race of people, the Macrocephali, who were characterized by very long heads. These long heads were thought to indicate nobility, so parents attempted to mold the soft skulls of their newborn to the desired shape.

> The characteristic was thus acquired at first by artificial means, but, as time passed, it became an inherited characteristic and the practice was no longer necessary. The seed comes from all parts of the body, healthy from the healthy parts and sickly from the sickly. If therefore bald parents usually have bald children, grey-eyed parents grey-eyed children, if squinting parents have squinting children, why should not long-headed parents have long-headed children. (Hippocrates, 1950, p. 103)

Hippocrates was also proposing the concept of the inheritance of acquired characteristics—a point of view that was to be adopted by Lamarck as the mechanism of evolutionary change—a theory accepted by many well into the 20th century.

Hippocrates's hypothesis for inheritance may not appear to be a monumental beginning—but it was. He identified a scientific problem (possibly the most difficult step of any), proposed an explanatory hypothesis, and wrote in a manner that we can understand. For such a scientific analysis to have occurred two and a half millennia ago is quite exceptional. The roots of the way we think about scientific phenomena go right back to the Greeks, even as much of our non-scientific mode of thought can be traced back to the ancient Hebrews (via the Hebrew and Christian bibles).

ARISTOTLE

Aristotle (384–322 B.C.) was active a century after Hippocrates. His *Generation of Animals* deals with problems of both genetics and development. This linking of two such seemingly disparate fields has a distinctly modern ring.

Aristotle assumed that there must be a *physical basis of inheritance* in the "semen" produced by the parents. This point, so obvious to us today, was basic to all future work. Inheritance need no longer be thought of as caused by some vague spirit or emotion but by a *substance* transmitted by the parent or parents. Little was known of the nature of this semen in the fourth century B.C. The modern understanding of gametes dates only to the 19th century A.D. Thus Aristotle used the term "semen" much as we would use the term "gametes," and not as a secretion of males that contains the sperm.

The problem, then, becomes understanding the nature of semen. Aristotle discusses the Pangenesis Theory of Inheritance in such a way that suggests the theory was widespread and probably generally accepted (however he was to reject it). He lists four major observations and arguments that support pangenesis as a probable hypothesis. First, noting that mating (in humans) gives pleasure to the whole body, he reasoned that the whole body must contribute to the semen. Second, there were observations suggesting that mutilations may be inherited. One such case came from Chalcedon (on the Bosporus in present-day Turkey) where a man was branded on the arm and his child, born subsequently, had a defect on the arm. Third, it was commonly observed that the offspring resemble parents not only in general but often in strikingly specific ways. Hence the specific characteristics could be assumed to produce specific substances that become part of the semen. And fourth, if semen for the whole can be produced, there is no reason why the specific parts of the body could not contribute to the semen as well.

Aristotle thought otherwise and rejected pangenesis. He suggested no comprehensive alternative but he did suggest a tentative hypothesis—that turns out to be the way we think today. Noting that children resemble parents not only in structure but also in such features as voice and gait, Aristotle asked how could non-structural features produce material for the semen. (You may find it interesting to ask students to deal with this argument of Aristotle as well as those to follow.) Then, too, babies of fathers with beards and gray hair are not similarly hirsute at birth. It had also been observed that children seem to inherit characteristics of more remote ancestors, who could hardly have contributed to the semen of their parents (how would we handle this observation today?). Thus a woman of Elis (in the northwest part of the Greek Peloponnese) had intercourse with a blackamoor (a term applied to any very dark-skinned individual). Her daughter was white but her grandson was black.

Even more important evidence that refuted pangenesis came from observations of the same general sort that were used to refute Darwin's Theory of Pangenesis more than two millennia later. It was well known that parts could easily be removed from plants, yet these mutilated plants could produce offspring that were perfect and entire. And then there was the awesome argument that if, as in humans, two parents produce the semen with the gemmules for all parts of the body, would we not expect offspring with two heads, four arms, etc.?

These and many other arguments and observations led Aristotle to reject pangenesis and to ask,

> Why not admit straight away that the semen . . . is such that out of it blood and flesh can be formed, instead of maintaining that semen is itself both blood and flesh? (Aristotle, 1943, p. 65)

This tentative hypothesis was to become the way we think today.

This is as far as Aristotle could advance our understanding of inheritance with the data and methodology of his time. He proposed a hypothesis, vague though it was, that in our day has proven to be true beyond all reasonable doubt. This hypothesis was to be the conceptual limit for the next two thousand years. The lack of progress in understanding inheritance was due mainly to an inability to formulate precise questions that could be studied with the available methodology.

AFTER ARISTOTLE

Interest in scientific questions almost ceased in the Western World throughout those long centuries when the Church held hegemony over the mind of man. It was not until well after the Renaissance that observation and experiment were applied in a systematic manner in an attempt to gain understanding of inheritance. Even then progress was exceedingly slow, again because it was impossible to find a productive question.

In the 18th and 19th centuries the standard way to seek information about inheritance was by cross-breeding. Individuals that differed from one another were crossed and offspring were studied. To this day this remains one of the most powerful procedures for obtaining information about inheritance. Nevertheless, it might be interesting to explore with your students what sorts of information could be expected from this approach. Such an exercise will be most valuable if one tries to answer the question, without considering what did in fact happen. It is hard to imagine discovering more than the pre-Mendelian breeders did discover: when differing individuals are crossed the offspring will usually be more or less intermediate or occasionally look more like one parent than the other.

In fact, so little progress was made before the closing decades of the 19th century in understanding inheritance that we may conclude that little of theoretical importance occurred between Aristotle (384–322 B.C.) and Charles Darwin (1809–1882 A.D.).

THE METHODS OF SCIENCE

This may seem surprising considering the widespread notion that there are set procedures in science—the scientific method—that, if dutifully followed, will lead inexorably to new discoveries and deeper understanding. These methods were formulated slowly by philosophers over the centuries, but as usual, it will be possible to emphasize the contributions of only a few individuals. We will begin with Sir Francis Bacon (1561–1626), Lord Chancellor of England. As de Solla Price (1975) put it, with deliberate hyperbole, "Francis Bacon plotted the [scientific] revolution and codified the scientific method."

FRANCIS BACON AND THE GREAT INSTAURATION

From Bacon on, biology lessened its emphasis on field work and natural history and increased its emphasis on laboratory observations and experimentation. There was much interest in the nature of science and in what came to be known as "the scientific method" for gaining knowledge of the natural world. The essence of the scientific method was its rejection of the classical and medieval-theological habit of starting the inquiry with a point of view that was accepted as true and then deducing the consequences. For example, the acceptance of the Judeo-Christian God as the creator of the universe and all its inhabitants provided a world view that had been accepted as adequate for centuries—and remains so for many today. It led to a very different view of nature than the one provided by modern science.

A diametrically opposed point of view began to develop as the Scientific Revolution emerged during the 16th and 17th centuries. Bacon's suggestion was to begin with data, not faith. That is, one should consider all known facts related to some natural phenomenon and try to formulate general principles to explain the facts. This logical method of reasoning from the particulars to the general is known as induction—a procedure that was to give us the modern world but its adherents were usually found offensive by those who preferred the established traditions of society, church, and state.

Bacon's suggestions for doing science are described in his *Instauratio Magna* of 1620. This was planned as a multi-volume work but only a small portion of it was published, the most notable being the *Novum Organum or True Suggestions for the Interpretation of Nature.* Even this was a preliminary abstract and consists of 129 aphorisms in Book I and 52 in Book II. The old "Organon" (Aristotle, 1955; Ross, 1949) consisted of the logical treatises of Aristotle, the procedures of which Bacon wished to replace.

His argument begins by pointing out the ineffectiveness of earlier attempts to understand nature. Bacon notes that, unless great care is taken, the things that the human mind imbibes tend to be "false, confused, and overhastily abstracted from the facts." In good measure this is a consequence of our observing what we have already assumed to be true. The consequence of this *a priori* approach is that "philosophy and the other intellectual sciences . . . stand like statues, worshipped and celebrated, but not moved or advanced." It is no wonder that our understanding of nature is "badly built up, and like some magnificent structure, without any foundation."

> Though all the wits of all the ages should meet together and combine and transmit their labours, yet will no great progress ever be made in science by means of anticipations [that is, by relying totally on preconceived ideas]; because radical errors in the first concoction of the mind are not to be cured by the excellence of functions and remedies subsequent. (*Novum Organum*, Book I, Aphorism 30)

Thus reliable knowledge of the natural world comes from observing nature herself and not from probing the human mind. Nature was to be the arbiter in Bacon's plan "to commence the total reconstruction of sciences, arts, and all human knowledge"—his "Great Instauration."

Thus one was to begin an investigation by assembling all the data from observation and experiment that related to the topic of the investigation. Great care had to be exercised lest erroneous information be included. That, of course, would lead to erroneous conclusions. Not only must the observations be made as accurately as possible but often "neither the naked hand nor the understanding left to itself can effect much. It is by instruments and helps [for the mind] that the work is done."

Snares of the mind: Idols to be abhorred

The mind must guard against preconceived ideas if observations are to be accurately interpreted. This is extraordinarily difficult to achieve since what we are, think, and do depends so greatly on our acceptance of the belief systems of the society in which we live and of the science that we profess. These belief systems become the idols to which we may submit, and to the extent we do, may lead to erroneous conclusions. Bacon lists four: the Idols of the Tribe, Cave, Market-Place, and Theatre. (Bertrand Russell recognizes still another, the Idols of the Schools [1945, p. 544].)

The Idols of the Tribe consist of the erroneous preconceived ideas and fuzzy thinking common to all human beings.

The Idols of the Cave are the erroneous beliefs of each individual's mind—the individual mind being like an isolated cave. He notes especially how individuals tend to favor their own opinions and discoveries—a serious problem for us to this day.

> Men become attached to certain particular sciences and speculations, either because they fancy themselves the authors and inventors thereof, or because they have bestowed the greatest pains upon them and become most habituated to them. But men of this kind, if they betake themselves to philosophy and contemplations of a general character, distort and colour them in obedience to their former fancies . . . . (Book I, Aphorism 54)

Other Idols of the Cave are an undue reverence for antiquity or for novelty.

> This however turns to the great injury of the sciences and philosophy; since these affectations of antiquity and novelty are the humours of partisans rather than judgments; and truth is to be sought not in the felicity of any age, which is an unstable thing, but in the light of nature and experience, which is eternal . . . . (Book I, Aphorism 56)

> And generally let every student of nature take this as a rule,—that whatever his mind seizes and dwells upon with peculiar satisfaction is to be held in suspicion . . . . (Book I, Aphorism 58)

The Idols of the Market-Place are the semantic problems that arise when people try to communicate and use words differently. The words of our language were developed for everyday use and, not infrequently, they are unsuitable or insufficiently specific for use in science.

The Idols of the Theatre, that is, of philosophical systems, consist mainly of adhering to those modes of thought in philosophy and theology where "truth" is deduced from *a priori* premises. He notes, for example, that some have attempted to found a system of natural philosophy (that is, natural science) on the first book of Genesis. He advises, however, that "We be soberminded, and give to faith that only which is faith's."

And there are more general problems, for it is not

> to be forgotten that in every age Natural Philosophy has had a troublesome adversary and hard to deal with; namely, superstition, and the blind and immoderate zeal of religion.

Or, most discouragingly, in schools and universities

> and similar bodies destined for the abode of learned men and the cultivation of learning, everything is found adverse to the progress of science . . . . But by far the greatest obstacle to the progress of science . . . is found in this—that men despair and think things impossible.

How to b a b

After these lengthy discussions of what he regarded as the procedural and philosophical errors of the past that made progress in science difficult or impossible, Bacon introduces his new approach by this charming metaphor.

> Those who have handled sciences have been either men of experiment or men of dogmas. The men of experiment are like the ant; they only collect and use: the reasoners resemble spiders, who make cobwebs out of their own substance. But the bee takes a middle course; it gathers its material from the flowers of the garden and the field, but transforms and digests it by a power of its own. Not unlike this is the true business of philosophy; for it neither relies solely or chiefly on the powers of the mind, nor does it take the matter which it gathers from natural history and mechanical experiments and lay it up in the memory whole, as it finds it; but it lays it up in the understanding altered and digested. Therefore from a closer and purer league between these two faculties, the experimental and the rational (such as has never yet been made) much may be hoped. (Book I, Aphorism 95)

It is not at all obvious, however, how one should try to be a bee. In Book II of *Novum Organum* he provides an example of what he has in mind by an analysis of what could be the true nature of heat. How is one to understand this phenomenon that is a constant feature of our ambient environment?

First, one should assemble all the readily available information about heat (or any other phenomenon to be investigated), so Bacon gives three tables of data. The Table of Existence and Presence enumerates many phenomena associated with heat: rays of the sun, meteors, thunderbolts, volcanic eruptions, flames, sparks, burning solids, quicklime sprinkled with water, horse-dung when fresh, strong wines, some spices, acid poured on the skin, and even intense cold.

A second Table of Deviation and Absences lists phenomena where we might expect heat but do not find it. For example he notes that although light in the form of the sun's rays are hot, light from the moon and stars is cold. Furthermore, there have been instances where a person's hair is surrounded by flames (now called St. Elmo's Fire) yet the hair does not burn.

The third Table of Degrees or Comparisons of Heat lists instances where the same item may differ in temperature. For example, plants are not warm to human touch but may become so if they are enclosed in a box or allowed to decay. The heat of animals is increased by exercise, wine, feasting, Venus, fever, and pain.

Induction

Now comes the truly extraordinary part of Bacon's analysis. It seems impossible that anyone could consider all these varied, often irrelevant, and dubious bits of data listed in his three tables and, by induction, arrive at an understanding of the basic phenomenon of heat. First he eliminates some possibilities. For example, light cannot be the basis of heat, since light from the moon and stars is not hot even though light from flames and the sun may be. Color cannot be the cause, since a red hot iron and the relatively cool flame of burning alcohol differ so much. Heat cannot be a substance, since iron and other materials may be made hot and not lose substance.

After ruling out many possibilities in this manner, Bacon reaches this astonishing conclusion:

> From instances taken collectively, as well as singly, the nature whose limit is heat appears to be *motion.* This is chiefly exhibited in flame, which is in constant motion, and in warm or boiling liquids, which are likewise in constant motion. It is also shown in the excitement or increase of heat by motion and by bellows and draughts . . . . It is also shown by the extinction of fire and heat upon any strong pressure, which restrains and puts a stop to motion . . . (thus is with tinder, or the burning snuff of a candle or lamp, or even hot charcoal cinders, for when they are squeezed by snuffers, or the foot, and the like, the effect of the fire instantly ceases) . . . . It is further shown by this circumstance, namely, that every substance is destroyed, or at least materially changed, by strong and powerful heat: whence it is clear that tumult and confusion are occasioned by heat, together with a violent motion in the internal parts of bodies, and this gradually tends to their dissolution . . . . It must not be thought that heat generates motion, or motion heat, (though in some respects this be true,) but that the very essence of heat . . . is motion and nothing else . . . . (*Novum Organum,* Book II, Aphorism 20)

The data available to Bacon were wholly inadequate for him to reach what we now accept as the correct view of the nature of heat. Furthermore, induction—the philosophical process that Bacon so valued—could not alone sort among all of Bacon's phenomena related to heat and conclude that heat is a form of motion. In this case a fine mind had made a lucky guess.

Perhaps the greatest weakness in Bacon's system was the lack of a clear indication of how to make the intellectual step from the isolated facts to the general statement. That remains the central difficulty of inductive reasoning to this day. It is here that genius, intuition, inspiration, serendipity, and luck—one or several—must assume control of the analysis.

Two and a half centuries later the great English scientist, John Tyndall (1863), had this to say:

> From the direct contemplation of some of the phenomena of heat, a profound mind is led almost instinctively to conclude that heat is a kind of motion. Bacon held a view of this kind . . . .

But the *sine qua non* is that profound mind.

Induction—hypothesis—deduction

Induction means no more than that one begins a study with observation and experimentation relating to some natural phenomena, and uses the data obtained in attempting to reach some understanding of fundamental causes or associations of seemingly unrelated events. Selected data are used to frame provisional hypotheses and from these hypotheses deductions are made and tested. Deduction remains a powerful adjunct of analysis but the deduction of modern scientists is not the same as the deductive reasoning that Bacon found so repugnant. In science today deductions from a hypothesis are (hopefully) necessary conclusions from that hypothesis. Their value is to suggest what observations or experiments can be done in order to confirm or deny the hypothesis, nothing more. The deductions of the early philosophers and theologians were often regarded as eternal conclusions drawn from eternal truths, but in reality they were based on shared faith or bold imagination, not on evidence.

To this day scientists strive to start only with the most reliable and confirmable data, and thereafter employ a constant interplay of inductive and deductive procedures to reach a more fundamental level of understanding of the natural world. That understanding can be no more than "this is the most accurate statement that can be made with the evidence at hand." It must be emphasized to students that this does not mean that the science of the day is "wrong." It means that the science of today will be replaced by a better science tomorrow. Our analysis of the development of genetic concepts will provide an excellent example. The genetics of Mendel of 1900 was not wrong. It was expanded in the better genetics of Sutton in 1903 and then that of Morgan in 1912, and finally into the vastly better genetics of today.

Some philosophers of science may maintain that Bacon was seriously inadequate in not appreciating the value of deductive reasoning. To be sure he was not as explicit as the philosophers of today but, considering the pioneer nature of his effort, one can argue that he comes off fairly well. For example,

> The signs for the interpretation of nature comprehend two divisions: the first regards the eliciting or creating of axioms from experiment, the second the deducing or deriving of new experiments from axioms. (*Novum Organum,* Book II, Aphorism 10)

If one substitutes "hypotheses" for "axioms" we find here not only a brief and elementary description of what philosophers of today recognize as important components of scientific methodology but about as accurate a statement as can be made of what working scientists actually do. And far from expecting scientific understanding to come solely from those ants collecting facts, Bacon suggests that with his approach

> we have good reason, therefore, to derive hope from a closer and purer alliance of these faculties, (the experimental and rational) than has yet been attempted. (Book I, Aphorism 95)

The English astronomer-chemist-photographer Sir John Herschel (1792–1871), himself an important student of scientific methods, recognized in Bacon the antecedents of the modern hypothetico-deductive method. Consider this one sentence quote:

> It is to our immortal countryman Bacon that we owe the broad announcement of this grand and fertile principle [induction]; and the development of the idea, that the whole of natural philosophy consists entirely of a series of inductive generalizations, commencing with the most circumstantially stated particulars, and carried up to universal laws, or axioms, which comprehend in their statements every subordinate degree of generality, and of a corresponding series of inverted reasoning from generals to particulars, by which these axioms are traced back to their remotest consequences, and all particular propositions deduced from them . . . . (Herschel, 1830, p. 104)

The fundamental difference between Bacon's approach and the approaches that he attacked was that scientific statements must be based on the data derived from observations and experiments of natural phenomena and not on preconceived principles, or beliefs of classical authors, or imagination, or superstition. As Bacon advises we

> should not arrogantly search for the sci-

> ences in the narrow cells of human wit, but humbly in the greater world.

Thus it is incorrect to say that Bacon believed that induction is the only effective procedure for arriving at acceptable scientific statements. His emphasis on induction was to counter the seemingly total reliance of philosophers and theologians on deductive reasoning from broadly-inclusive *a priori* beliefs. Induction is not an automatic procedure for advancing science. It depends absolutely on the brilliance, perseverance, knowledge, and luck of the scientist. And deduction is an effective and powerful procedure when one uses it to make testable deductions from provisional hypotheses.

The legacy of Sir Francis Bacon, Lord Chancellor of England, is that we must study nature, not books alone, and cease the worship of those four Idols. Scientists of the 17th century—William Gilbert, Andreas Vesalius, Galileo Galilei, Johann Kepler, and William Harvey—were attempting to do these things. Bacon was most valuable in being a publicist and codifer of the Great Instauration—a new way for obtaining reliable information about the natural world.

References to Bacon

The standard edition of Bacon's works is that of Spedding, Ellis, and Heath (1857–1874) but Montagu (1851) is clearer at times. For a Latin edition of *Novum Organum* see also Fowler (1889). Selections, often with notes, are provided by Crombie (1959), Dick (1955), McClure (1928), and Robertson (1905). For evaluations of Bacon see W. T. Jones (1952), Liebig (1863), Macaulay (1837), Randall (1926), Russell (1945), and A. E. Taylor (1927, 1934).

DARWIN AND THE REBIRTH OF PANGENESIS

Darwin is an especially instructive example of a pre-Mendelian attempting to explain inheritance and we can see some of the reasons why so little progress was made. Darwin is recognized, after all, as a person of tremendous ability, not only for his *On the Origin of Species* but for fundamental investigations on a broad range of biological subjects as varied as coral reefs, habits of earthworms, taxonomy of barnacles both living and fossil, and the fertilization of orchids. His attempts to understand inheritance gave us the longest of his works—the two volumes of *The Variation of Animals and Plants under Domestication* (1868).

Initiating the inquiry

Darwin's problem was the same as for all who sought a rent in the veil of ignorance that enmeshed the subject of inheritance: how could one properly initiate the inquiry?

It was exceedingly important that he do so and achieve some level of success. His momentous theory of the origin of species by means of natural selection depended totally on a constant supply of new variants that persisted generation after generation and upon which selection could act. In the absence of new variants, evolutionary change would be impossible. And Darwin notes, "it is obvious that a variation which is not inherited throws no light on the derivation of species, nor is of any service to man" (vol. 2, p. 1; unless noted otherwise all of the references in this section will be to the 1868 edition of *The Variation of Animals and Plants under Domestication*).

Not everyone in the mid-19th century believed that the inheritance of minute differences was either of much importance or subject to rigorous rules. There was no need to do so if one accepted the prevailing and socially-mandated view that each kind of organism had been separately created by the Judeo-Christian God and if one noted the seemingly stochastic nature of inheritance. Possibly the main reason that individuals differed from one another was due to the environment.

The subject was thought fuzzy even by Darwin. He wrote:

> When a new character arises, whatever its nature may be, it generally tends to be inherited, at least in a temporary and sometimes in a most persistent manner. (vol. 2, p. 2)

Darwin had considerable first-hand expe-

FIG. 1. The hand of the Porcupine Man. (H. Baker, 1756)

rience with crossing plants and animals, especially pigeons, and through correspondence and reading he had an extensive knowledge of the results of others. He was convinced that inheritance must be a phenomenon that is widespread, somewhat precise, and important.

The Porcupine Man

Darwin's fine eye for the critical observation or test led him to lay great emphasis on some remarkable examples of inheritance that were so unusual that neither chance nor environment seemed adequate explanations. One of the more spectacular instances was the strange story of the "Porcupine Man" (Fig. 1).

In 1733 Machin reported to the Royal Society a strange case of Edward Lambert, then in his teens. He was the son of a laborer who lived in Suffolk.

> His skin (if it might be so called) seemed rather like a dusky coloured thick case, exactly fitting every part of his body, made of a rugged bark, or hide, with bristles in some places, which case covered the whole excepting the face, the palms of the hands, and the soles of the feet, caused an appearance as if those

> parts were naked, and the rest clothed. It did not bleed when cut or scarified, being callous and insensible. It said he shed it once every year, about autumn, at which time it usually grows to a thickness of three quarters of an inch, and then is thrust off by the new skin which is coming up underneath.

Young Edward seemed entirely healthy and normal in all other respects. His father reported that Edward had normal skin at birth but at about two months it began to change. The baby had not been sick and there was no obvious cause. The mother had received no fright while with child. None of the sibs exhibited the abnormality.

In 1756 H. Baker provided a later report. By then Edward Lambert was a married man. He had one surviving son with the defect. A total of six sons had shown the defect but five had died. Baker reported that when the hand is drawn across the victim's skin it made a rustling noise. Subsequently two of the grandchildren showed the same defect and, according to Darwin, eventually four generations were observed with the defect—always restricted to males (vol. 2, p. 4).

As an aside, it can be noted that the modern medical term for this defect is ichthyosis hystrix gravior. Until recently it was believed that the condition is controlled by an allele on the Y-chromosome, since it was thought to affect males only. Stern reviewed the case and found that there may have been a daughter with the abnormality, hence the case for Y-chromosome transmission is in doubt. See Gates (1946), Stern (1957, 1973), F. Vogel and Motulsky (1979), and especially Penrose and Stern (1958) for illustrations and the account of the effort to discover more about the Lambert family. Thus the evidence available to Darwin may have been faulty in some respects but it was adequate for his purposes, namely to suggest that there is something that is inherited.

What is inherited?

How is one to account for these exceedingly rare events, so atypical of what is usually observed? Was it merely a matter of chance (whatever that might mean) or was it the result of some undetected environmental influence? Darwin regarded this and similar instances as evidence that "something" was transmitted from parent to offspring:

> When we reflect that certain extraordinary peculiarities have thus appeared in a single individual out of many millions, all exposed in the same country to the same general conditions of life, and, again, that the same extraordinary peculiarity has sometimes appeared in individuals living under widely different conditions of life, we are driven to conclude that such peculiarities are not directly due to the action of surrounding conditions, but to unknown laws acting on the organisation or constitution of the individual;—that their production stands in hardly closer relation to the conditions than does life itself. If this be so, and the occurrence of the same unusual character in the child and parent cannot be attributed to both having been exposed to the same unusual conditions, then the following problem is worth consideration, as showing that the result cannot be due, as some authors have supposed, to mere coincidence, but must be consequent on the members of the same family inheriting something in common in their constitution. Let it be assumed that, in a large population, a particular affection occurs on an average in one out of a million, so that *a priori* chance that an individual taken at random will be so affected is only one in a million. Let the population consist of sixty million, composed, we will assume, of ten million families, each containing six members. On these data, Professor Stokes has calculated for me that the odds will be no less than 8333 millions to 1 that in the ten million families there will not be even a single family in which one parent and two children will be affected by the peculiarity in question. But numerous cases could be given, in which several children have been affected by the same rare peculiarity with one of their parents; and

> in this case, more especially if the grandchildren be included in the calculation, the odds against mere coincidence become something prodigious, almost beyond enumeration. (vol. 2, pp. 4–5)

Even today it would be hard to supply better arguments that "something" had been transmitted from Edward Lambert to his sons. It was most unlikely that the skin condition was a consequence of an environmental stimulus or of chance. If there was a physical basis for the inheritance of the porcupine-skin condition and similar variations, it should be possible to discover laws governing their transmission.

Assembling the data

Darwin set about to discover these laws with the accepted procedures of his time but, as we shall see, entirely different approaches would be needed to illuminate that black-box of inheritance. He tells us in his autobiography how he began his great study:

> After my return to England [in 1836 at the end of the voyage of the *Beagle*] it appeared to me that by following the example of Lyell in Geology, and by collecting all facts which bore in any way on the variation of animals and plants under domestication and nature, some light might perhaps be thrown on the whole subject. My first note-book was opened in July 1837. I worked on true Baconian principles, and without any theory collected facts on a wholesale scale, more especially with respect to domesticated productions, by printed enquiries, by conversations with skilful breeders and gardeners, and by extensive reading. (Barlow, 1958, p. 119)

And he did record a prodigious amount of information related to "domesticated productions." Roughly half of *Variation* provides information on the presumed origin of domesticated plants and animals from wild ancestors. It was assumed that this had involved the selection by human beings of the hereditary variations that were thought desirable. Starting with domesticated dogs and cats, he went on to assemble the available data for horses, asses, pigs, cattle, sheep, goats, rabbits, pigeons, chickens, ducks, geese, peacocks, turkeys, canaries, goldfish, honey bees, silk moths, the common cereals, garden vegetables, and fruits. All made sense with the assumption that rapidly-acting artificial selection by human beings was a counterpart of the excruciatingly slow natural selection that accounted for the origin of species.

Then there is a wealth of observations on inheritance in the more restricted sense. The following quotations will show the flavor of the results of his Baconian collection of data.

> Brothers and sisters of the same family are frequently affected, often at about the same age, by the same peculiar disease, not known to have previously occurred in the family. (vol. 2, p. 17)

> A rabbit produced in a litter a young animal having only one ear; and from this animal a breed was formed which steadily produced one-eared rabbits. (vol. 2, p. 12)

> I have been assured by breeders of the canary-bird that to get a good jonquil-coloured bird it does not answer to pair two jonquils, as the colour then comes out too strong, or is even brown. (vol. 2, pp. 21–22)

After your students have mastered Mendelian genetics, it may be interesting to them to suggest hypotheses to account for observations such as the one just given and that on chickens below.

> I have been assured by three medical men of the Jewish faith that circumcision, which has been practiced for so many ages, has produced no inherited effect. (vol. 2, p. 23)

But then Darwin goes on to quote an authority who suggests that there has been an effect.

> Nevertheless, Dr. Prosper Lucas has given, on good authorities, such a long list of inherited injuries, that it is difficult not to believe in them. (vol. 2, p. 23)

> In one lot of eleven mixed [chicken] eggs from the white Game and white Cochin by the black Spanish cock, seven of the chickens were white, and only four black: I mention this fact to show that whiteness of plumage is strongly inherited. (vol. 1, p. 240)

Darwin recorded numerous examples of observations that, in the years after 1900, were to be critical to the advancement of our understanding of inheritance. The next two quotations give accurate descriptions of what came to be known as sex-linked inheritance.

> Colour-blindness, from some unknown cause, shows itself much oftener in males than in females; . . . but it is eminently liable to be transmitted through women. (vol. 2, p. 72)

> Generally with the haemorrhagic diathesis [=hemophilia], and often with colour-blindness, and in some other cases, the sons never inherit the peculiarity directly from their fathers, but the daughters, and the daughters alone, transmit the latent tendency, so that the sons of the daughters alone exhibit it. Thus, the father, grandson, and the great-great-grandson will exhibit the peculiarity,—the grandmother, daughter, and great-granddaughter having transmitted it in a latent state. (vol. 2, p. 73)

The following quotation is of extraordinary interest in describing phenomena that were to become the core of Mendelian inheritance.

> As a general rule, crossed offspring in the first generation are nearly intermediate between their parents, but the grandchildren and succeeding generations continually revert, in a greater or lesser degree, to one or both of their progenitors. Several authors have maintained that hybrids and mongrels include all the characters of both parents, not fused together, but merely mingled in different proportions in different parts of the body; or, as Naudin has expressed it, a hybrid is a living mosaic-work, in which the eye cannot distinguish the discordant elements, so completely are they intermingled. We can hardly doubt that, in a certain sense, this is true, as when we behold in a hybrid the elements of both species segregating themselves . . . . Naudin further believes that the segregation of the two specific elements or essences is eminently liable to occur in the male and female reproductive matter; and he thus explains the almost universal tendency to reversion in successive hybrid generations. (vol. 2, pp. 48–49)

The phenomena to be explained

After this systematic and extensive survey of the information on inheritance, Darwin attempted to formulate a hypothesis to account for all the data. The main classes of phenomena that must be explained by a comprehensive hypothesis of inheritance were as follows.

1. *Some characteristics are inherited.* Most of these inherited features involved structures such as body size, color patterns, and an endless list of minor variations. Physiological characteristics were also inherited—such as color blindness and hemophilia. The inherited characteristic might be large or small, important or unimportant. He concluded, as quoted before, "When a new character arises, whatever its nature may be, it generally tends to be inherited, at least in a temporary and sometimes in a most persistent manner" (vol. 2, p. 2); in short, a capricious phenomenon. Any useful hypothesis would have to explain why features are inherited sometimes but not always.

2. *The inheritance, or not, of mutilations.* Some human societies habitually knock out teeth, perforate ears or nostrils, circumcise male babies, cut off a finger or two, yet their children do not show corresponding defects. There were other cases where it appeared that mutilations were inherited and they were given on such good authority that Darwin found "it difficult not to believe them." Several times Darwin referred to the case of "a cow that had lost a horn from an accident with consequent suppuration, produced three calves which

were hornless on the same side of the head" (vol. 2, p. 23). He concluded, "with respect to the inheritance of structures mutilated by injuries or altered by disease it is difficult to come to any definite conclusion" (vol. 2, pp. 22–23).

3. *Atavism.* This is the occurrence in an individual of some characteristic not expressed in the immediate forebears but believed to have been present in remote ancestors. For example, it was believed that the wild ancestors of the domesticated sheep had been black. Thus, when a black lamb appeared in a flock of carefully bred white sheep, it was explained as the persistence of some long-dormant hereditary feature.

4. *Sex-linked inheritance.* So far as the data went, it appeared that in most cases characters appeared to be inherited with equal facility from either parent. Nevertheless, Darwin knew of some where this was not the case. The examples of color blindness and hemophilia have been given already. Darwin drew an interesting conclusion from these cases, "We thus learn, and the fact is an important one, that transmission and development are distinct powers" (vol. 2, p. 84).

5. *Inbreeding.* If two organisms are crossed and their offspring bred with one another generation after generation, we speak of this as inbreeding. The usual result was the production of a relatively homogeneous population:

> When two breeds are crossed their characteristics usually become intimately fused together; but some characters refuse to blend, and are transmitted in an unmodified state either from both parents or from one. When grey mice are paired, the young are not piebald nor of an intermediate tint, but are pure white or of the ordinary grey colour . . . . In breeding Game fowls, a great authority, Mr. J. Douglas, remarks, "I may here state a strange fact: if you cross a black with a white game, you get both breeds of the clearest colours." Sir R. Heron crossed during many years white, black, brown, and fawn-coloured Angora rabbits, and never once got these colours mingled in the same animal, but often all four colours in the same litter. (vol. 2, p. 92)

Once again, the data of inheritance seemed to conform to no obvious rules or regularities. Any comprehensive hypothesis to explain the data would have to be adjusted to this difficult fact.

6. *Artificial selection.* Selection, either deliberate or unintentional, is a method that produces varieties of plants and animals of greater usefulness to human beings. It has been employed since the earliest days of agriculture. If a farmer desires to increase the size of chickens, and hence the quantity of food, he selects the largest hens and cocks to be the parents. In each generation he continues the same selection. With this procedure it is usually possible to develop animals or plants with the desired characteristics in a few generations. One of the most puzzling aspects of selection was the ability to produce individuals with characteristics not present in the ancestral population. For example, Darwin's favorite material, pigeons, had been selected to produce the most unusual breeds—entirely different from the ancestral rock dove of Europe. Selection could create something new. It was clear that artificial selection could, in a few generations, produce varieties that differed as much from one another in structural details as did the various wild species of the same genus or even species of different genera.

7. *The causes of variability.* "The subject is an obscure one; but it may be useful to probe our ignorance. Some authors . . . look at variability as a necessary contingent on reproduction, as much an aboriginal law, as growth or inheritance" (vol. 2, p. 250). Darwin believed that all domestic and wild species are variable. The differences are especially obvious in the domestic species where many unique varieties have been selected (Darwin found a report in the literature of a Dutch florist who kept 1,200 varieties of hyacinth). "Changes of any kind in the conditions of life, even extremely slight changes, often suffice to cause variability. Excess of nutriment is perhaps the most efficient single exciting cause" (vol.

2, p. 270). The kind of variation depends "in a far higher degree on the nature or constitution of the being, than on the nature of the changed conditions" (vol. 2, p. 250). (This last quote is one of numerous examples of the uncanny ability of Darwin to rise above the confusion of his time and see clearly what future research would establish.

8. *Regeneration.* When the tail or legs of salamanders are cut off, the lost structures are replaced. The ability to regenerate lost parts is common in many animals and plants and the events often resemble those in embryonic development. Darwin realized that both the formation of structures in development and the replacement of lost parts must have a hereditary basis since in both phenomena the final structures were characteristic of the species.

9. *Mode of reproduction.* Some organisms, such as *Hydra,* reproduce by asexual and sexual means. The *Hydra* that develops from a fertilized ovum is identical with that originating from an asexual bud. Thus, what is passed from parents to the offspring could not be restricted to the eggs and sperm—the ordinary cells of the *Hydra*'s body wall that formed the new individual asexually could also transmit the hereditary information. It is noteworthy that Darwin realized that any comprehensive theory of inheritance would have to account both for regeneration and the various patterns of development, including those species where the life cycle consists of two or more different stages.

10. *Delayed-action inheritance.* The details of fertilization in plants were poorly understood in Darwin's time and he was puzzled by the fact that the pollen affected not only the "germ" but some of the material tissues as well.

> If we could imagine the same flower to yield seeds during successive years, then it would not be very surprising that a flower of which the ovarium had been modified by foreign pollen should next year produce, when self-fertilised, offspring modified by the previous male influence. (vol. 1, p. 403)

Then there was the case of Lord Morton's Arabian chestnut mare. This mare was crossed to a species of zebra, the now extinct quagga. The foal of this union was intermediate in form and color. The mare was then sent to another farm where she was bred with a black Arabian stallion. There were two offspring.

> These colts were partially dun-coloured, and were striped on the legs more plainly than the real hybrid, or even than the quagga. One of the two colts had its neck and some other parts of its body plainly marked with stripes. Stripes on the body, not to mention those on the legs, and dun-colour, are extremely rare . . . . But what makes the case still more striking is that the hair of the mane in these colts resembled that of the quagga, being short, stiff, and upright. Hence there could be no doubt that the quagga affected the character of the offspring subsequently begot by the black Arabian horse. (vol. 1, p. 404)

There would certainly be a great deal of doubt about this observation today and, if true, the explanation would be entirely different. Darwin regarded these examples of delayed-action inheritance as "of the highest theoretical importance" and they, as much as anything else, were to be the cause of his flawed hypothesis for inheritance.

Formulating the hypothesis by induction

Any useful hypothesis to explain inheritance would have to account for the ten classes of data just enumerated. No obvious hypothesis emerges from the data, so one must engage in an exercise not unlike Bacon's arranging his data in three tables, eliminating some of the data, and of formulating the hypothesis from what remained.

It should be an interesting experience to have your students see what tentative conclusions they could reach solely on the basis of the ten classes of observations just given. Here are examples of how one might reason.

A. Since there are so many observations showing that offspring may resemble parents not only in general features but at times in very specific characteristics, one must conclude that there is some physical basis for inheritance. This is suggested by class 1 above and is not negated by any of the other nine classes of data.

B. Since the only physical link between generations of those organisms that liberate eggs and sperm that unite outside of the body are these gametes, all of the hereditary factors must be contained in the gametes.

C. The gametes cannot be the sole possessor of the hereditary factors, since in some organisms apparently identical offspring can be produced by sexual and asexual means (class 9).

D. The observations on the regeneration of lost parts (class 8), together with point C, suggest that many (most?, all?) cells of the body contain all of the hereditary factors.

E. The hereditary factors may be present but are not expressed either on a short-term basis (parents not exhibiting the features while grandparents and grandchildren do) or on a long-term basis (atavism, class 3). This strongly suggests that the hereditary factors are relatively permanent and stable even when they are latent.

F. The hereditary factors may change or entirely new ones may be formed, as in cases of the sudden appearance of entirely new variations.

G. Since the hereditary factors are present generation after generation, there must be some mechanism for their replication.

H. The hereditary factors may act in a manner similar to infectious agents in that those of one individual may invade the cells of another—as with Lord Morton's mare (class 10).

Thus we may tentatively conclude that there are hereditary factors and that these are present in at least many of the cells; they may be transmitted via the gametes, may be expressed or remain dormant in a given generation, can persist unchanged for generations, may change under some unknown conditions, and are capable of increasing in number. All of this agrees with what we know today about genes.

Class H, however, is clearly not part of modern genetics—the hereditary factors, the genes, of higher plants and animals do not normally go wandering around the body. We now know that the case was misinterpreted—there was no contamination of Lord Morton's mare by the semen of the quagga. Similar barring was found to occur in the offspring of Arabian and English race horses (Ewart, 1901; Burkhardt, 1979; Gould, 1983, ch. 30). Darwin was unaware of this and believing the report to be true was one important factor in making his hypothesis defective.

The hypothesis of pangenesis

How could one unite the heterogeneous data on inheritance into a single conceptual scheme? Darwin made the attempt.

> As Whewell, the historian of the inductive sciences, remarks:—"Hypotheses may often be of service to science, when they involve a certain portion of incompleteness, and even of error." Under this point of view I venture to advance the hypothesis of Pangenesis, which implies that the whole organization, in the sense of every separate atom or unit, reproduces itself. (vol. 2, pp. 357–358)

Darwin calls these minute units of reproduction the gemmules. Gemmules were assumed to possess the following characteristics: each and every part of an organism, and even parts of cells, were assumed to produce gemmules of specific types. These were capable of moving throughout the body so that all parts of the body, including the eggs and sperm, would contain gemmules of all types, *i.e.*, they would contain all of the hereditary factors. During development the gemmules unite with one another or with partially formed cells to produce new cells of the sort that had produced them. New gemmules were assumed to be produced continually. Gemmules were usually active in the offspring but they might remain dormant for generations.

Explaining the data

It was possible to explain each of the ten classes of phenomena that required explanation with Darwin's hypothesis of pangenesis as follows.

1. The transmission of characteristics

from parent to offspring was explained as a consequence of the production of the specific gemmules in the parental body, their incorporation in gametes, and their development in the offspring. Edward Lambert's skin cells had produced porcupine-skin gemmules and these were passed to his offspring via his sperm.

2. Mutilations are usually not inherited since gemmules for the normal structure would have been produced before the mutilation. Thus, the regeneration of a salamander's leg is possible because the leg gemmules were already present throughout the body, and after amputation could be assembled to produce a new leg. The few cases in which mutilations appeared to be inherited seemed to involve diseased parts. Darwin explained these cases as follows:

> In this case it may be conjectured that the gemmules of the lost part were gradually all attracted by the partially diseased surface, and thus perished. (vol. 2, p. 398)

3. Atavism was explained as a consequence of long-dormant gemmules becoming active after the passage of many generations. This was an especially gratuitous assumption. No more is being said than the following—since some characteristics seem to reappear in a lineage after not having been present for many generations, and if characteristics are determined by gemmules, then the gemmules must have been dormant—certainly a circular argument.

4. Sex-linked inheritance is a consequence of gemmules being dormant in one sex. Thus a color-blind man transmits color-blind gemmules to his daughter, where they remain dormant. She transmits the color-blind gemmules to her sons where they develop and result in color blindness.

5. The usually observed blending when two different forms are crossed is a consequence of the gemmules of each parent being mixed in the offspring. Those cases in which the characteristics of one parent dominate is a consequence of that parent's gemmules "having some advantage in number, affinity, or vigour over those derived from the other parent."

6. Artificial selection is possible because, by choosing individuals with desirable characteristics, one chooses as parents those individuals with the desirable gemmules. By continuous inbreeding of parents with the desired characteristics, one can slowly perfect a variety of the sort required.

7. The origins of variability were obscure but somehow the environment must be the cause—but not in a simplistic Lamarckian sense. But once a new variation appeared, new sorts of gemmules would then be formed. This implies that somatic cells can influence the hereditary composition of the germ cells—a point of view that, much later, was to be regarded as a most serious genetic heresy.

8. Regeneration could be accounted for since the gemmules for all structures are found throughout the body so any portion has the gemmules to replace the lost parts.

9. The identical outcome of sexual and asexual reproduction finds the explanation also in that all parts of the body having gemmules for all parts. The gametes of *Hydra*, as well as the cells of the body wall that are about to produce a bud, have the same library of gemmules.

10. Gemmules from that quagga male passed to Lord Morton's mare via the semen, entered the ovary, and reappeared and expressed themselves when the mare was mated to the Arabian stallion.

What can we say? Darwin had performed a great service in assembling a huge mass of data and, in a real sense, he had defined the field of heredity. His hypothesis of pangenesis was a notable advance over the hypothesis of pangenesis proposed by Hippocrates more than two millennia earlier. His most important contribution may have been his emphasis that inheritance has a physical basis and perhaps rules could be discovered for its mechanisms. He realized the weakness of his hypothesis of pangenesis but he had tried to bring order where none existed. If his efforts served no other purpose they at least gave other scientists a place to start, a catalog of the sorts of data to be explained by any comprehensive theory of inheritance, a discussion of the main problems, and a hypothesis that could be tested.

Galton's rabbits

Charles Darwin's nephew, Francis Galton (1822–1911), had long been interested in his uncle's work and saw a way to test the hypothesis of pangenesis. In 1871, three years after the publication of *Variation . . .* , he presented a fascinating paper before the Royal Society. He began,

> Darwin's provisional theory of Pangenesis claims our belief on the ground that it is the only theory which explains, by a single law, the numerous phenomena allied to simple reproduction, such as reversion, growth, and repair of injuries. On the other hand, its postulates are hypothetical and large, so that few naturalists seem willing to grant them. To myself, as a student of Heredity, it seemed of pressing importance that these postulates should be tested. If their truth could be established, the influence of Pangenesis on the study of heredity would be immense; if otherwise the negative conclusion would still be a positive gain. (Galton, 1871*a*)

His test was simple and direct. He knew that blood could be transferred from one animal to another and that "it was not a cruel operation." He proposed to transfer blood between different strains of anesthetized rabbits and then study their offspring. Thus, if blood of black rabbits was injected into silver-grey rabbits and the silver-greys then bred with one another, one could ascertain if the blood of the black rabbits had any effect.

> If Pangenesis were true . . . the results would be startling in their novelty, and of no small practical use; for it would be possible to modify varieties of animals, by introducing slight dashes of new blood, in ways important to breeders.

Galton found that his experimental rabbits all bred true. There was no evidence that the injected blood modified the offspring of those receiving it.

Darwin reacted promptly (1871) to this attack on his hypothesis, maintaining that Galton's experiments were no test at all since he "had not said one word about the blood" and "It is, indeed, obvious that the presence of gemmules in the blood can form no necessary part of my hypothesis," since gemmules were assumed to exist in creatures lacking a circulatory system.

This was, indeed, a strange rejoinder: if gemmules were present throughout the body, surely they would be present in blood. Possibly Darwin was having troubles with the Idols of the Cave.

Galton replied (1871*b*) with mock contrition, saying how sorry he was to have misinterpreted what his uncle had said.

Pangenesis evaluated

Darwin's hypothesis of pangenesis was based on gemmules but he had no evidence for their existence. They were invented to account for the observed phenomena of inheritance. This is legitimate scientific procedure. Atoms were invented to account for the data of chemistry; a planet later named Pluto was invented to account for irregularities in the orbits of the known planets. Atom and Pluto were useful hypotheses long before their reality was established.

The weakness of the hypothesis of pangenesis was that it did not simplify heredity. Darwin listed the ways that inheritance works and then held that it works that way because the gemmules acted that way. This was the same as saying that "heredity" = "gemmules" and, since "gemmules" were entirely hypothetical, little was gained by ascribing such important functions to them. In Darwin's time the term "heredity" would have sufficed. The hypothesis was not well regarded, even though there was not a better one to take its place. As Vorzimmer (1970, p. 257) was to write years later, the hypothesis of pangenesis was "so *ad hoc* as to withstand any criticism which sought to point up any fact inconsistent with it."

It can also be maintained that, when Darwin wrote, there was no possibility of anyone developing a concept to explain all of the data of inheritance. This was especially true when some of the "facts" that Darwin thought most important were later found to be erroneous. Biologists would have to reach the stage of genetic engineering before they could do to Lord Morton's mare what that quagga was thought to have done.

As this story unfolds we will find that after 1900 genetics made great progress by first trying to explain very little and then, as confirmable hypotheses were developed, more and more puzzlements were studied, explained, and incorporated into the corpus of genetic theory. A remark of Hardin (1985, p. 4), made in another connection is fully relevant here: "What began as knowledge about very little turns out to be wisdom about a great deal." Darwin began by trying to explain a great deal and ended by explaining very little.

CROP IMPROVEMENT BEFORE GENETICS

Genetics is much cherished today because it provides so much practical knowledge and methods for producing better varieties of cultivated plants and domesticated animals. Genetics began to become a rigorous science only in 1900, so it is astonishing to note that all of the important animal and plant crops had been domesticated and largely perfected before Darwin published *The Variation of Animals and Plants under Domestication* in 1868. In fact, far more was accomplished in the long ages of seeming ignorance of genetics than in the first half of the 20th century when genetics blossomed with new concepts and techniques.

There was great interest in England, in Darwin's time and earlier, in improving agriculture. This was a period when social status depended primarily on the ownership of land and far less on one's position in business or industry. Many of the lords of the manor, when not otherwise occupied producing episodes for *Masterpiece Theater*, paid special attention to the careful breeding of plants and animals. Much of the data in *Variation* came from these efforts. Darwin describes the approach,

> The effects of free or uncontrolled breeding between the members of the same variety or of closely allied varieties are important; but are so obvious that they need not be discussed at length. It is free intercrossing which chiefly gives uniformity, both under nature and under domestication, to the individuals of the same species or variety, when they live mingled together and are not exposed to any cause inducing excessive variability. The prevention of free crossing, and the intentional matching of individual animals, are the corner-stones of the breeder's art. No man in his senses would expect to improve or modify a breed in any particular manner, or keep an old breed true and distinct, unless he separated his animals. (vol. 2, p. 85)

Thus, with care, a breeder could perfect varieties for different conditions of soil and climate. In the case of sheep,

> The several races have become adapted to different kinds of pasture and climate: for instance, no one can rear Leicester sheep on mountainous regions, where Cheviots flourish. As Youatt has remarked, "in all the different districts of Great Britain we find various breeds of sheep beautifully adapted to the locality which they occupy. No one knows their origin; they are indigenous to the soil, climate, pasturage, and the locality on which they graze; they seem to have been formed for it and by it." Marshall relates that a flock of heavy Lincolnshire and light Norfolk sheep which had been bred together in a large sheep-walk, part of which was low, rich, and moist, and another part high and dry, with benty grass, when turned out, regularly separated from each other; the heavy sheep drawing off to the rich soil, and the lighter sheep to their own soil; so that "whilst there was plenty of grass the two breeds kept themselves as distinct as rooks and pigeons." (vol. 1, p. 96)

The development of domesticated varieties from wild ancestors is no more than evolution guided by both natural and artificial selection. Furthermore it involves the primary factor leading to speciation in nature—geographic isolation. To be sure, the cause of the geographic isolation might be no more than the fence surrounding a farm but a well-kept fence is entirely effective in preventing gene flow.

Evolution in nature is normally exceedingly slow, except in those cases where the natural population is confronted by an entirely new environmental challenge such as pesticides, antibiotics, and industrial pollution. It is slow only because we normally observe the natural population *after* it has been subjected to selection for generations. By the time we observe the natural population the possibilities of what can be accomplished with the gene pool of the moment interacting with the environment of the moment will have been explored and the population will have achieved a level of perfection that permits survival.

While natural selection need do no more for the population than permit survival, artificial selection can accomplish much else. In domestication, evolution is driven by human goals. Domestication does not result in a better sheep for sheep's sake. It results in sheep with better wool, better flesh, greater ability to survive where the farmer wishes it to survive, and greater fecundity—all for the farmer's benefit. It may even produce a type of animal having great difficulty surviving under natural conditions. Hogs are bred for what must be uncomfortable obesity. Some varieties of dogs are bred for abnormalities of the skull that make breathing difficult and noisy. Some varieties of pigeons are selected for central nervous system defects that produce highly abnormal behavior patterns.

Evolution under domestication is rapid because new goals are set for the genome and selection is exceedingly severe—generation after generation for a few desirable parents become the sole progenitors for the subsequent generations. The pre-Mendelian breeders also knew how to increase variability over that as we know today to be associated with chromosomal crossing-over. They did this by crossing markedly different varieties (sometimes even different species) knowing from experience that the second and later generations would usually be highly variable. Not infrequently seemingly new types appeared and these would offer new possibilities for selection.

Thus human beings had been using sound genetic and evolutionary principles since the Neolithic when our ancestors began to abandon the chase and started to settle down. It required neither the insights of Darwin nor those of Mendel for our ancestors to have given us *all* the plant species that we now commonly use for food, fiber, work, and pleasure.

Nevertheless we are, at this moment, about to enter a new era when the techniques of modern biology can permit a notable improvement in our ability to mold animals and plants to human needs.

REFERENCES

The following references introduce the vast literature of attempts to understand inheritance in the pre-Mendelian centuries. These references are mainly those concerned with using the data of animal and plant breeding to understanding inheritance. References to those who attempted to understand inheritance through studies of gametes and fertilization will be given later.

Babcock (1949–1951), Bailey (1895), Barthelmess (1952), Cole (1930), Darlington (1969), Darwin (1868), Dunn (1965*a*, 1965*b*, 1969), Focke (1881), Froggatt and Nevin (1972), Galton (1889), Gasking (1967), Ghiselin (1969), Glass (1947, 1959*a*, 1959*b*), Lithgow (1889), Mayr (*1973 [included in 1976], 1976, *1982), Mitchell (1910–1911), Moore (1972*a*, 1972*b*), Needham (1959), Olby (1963, *1966), Pearson (1924), Roberts (1929), Sachs (1890), Stubbe (*1965), Sturtevant (1965*a*), Vernon (1903), Vorzimmer (1963, 1970), and Zirkle (1935*a*, 1935*b*, 1936, 1946, 1951*a*, 1951*b*).

TWIN APPROACHES TO STUDYING INHERITANCE

Two main research approaches were of prime importance in gaining an understanding of inheritance. So far we have considered only one—breeding. Organisms were crossed and the offspring studied. One then attempted to develop hypotheses about the mechanisms of inheritance from the data obtained. This was Darwin's approach but neither he nor others in the last half of the 19th century were able to advance our understanding very much.

The other line of research was based on

this analysis: There is a structural bottleneck in the life cycle of both animals and plants. The two sexes usually produce small eggs and always very small sperm and these combine to produce the individuals of the next generation. At least in some species, there is no further contact between parents and offspring so whatever hereditary information is transmitted must be in the gametes.

This last argument could not be extended to all species. In mammals and seed plants, for example, the early stages of development of the offspring occur in close relation to the maternal tissues. There would be a distinct possibility, therefore, of a maternal influence during early development. Nevertheless, one could follow Bacon and decide that, since there can be no maternal influence after fertilization in some species, such maternal influence cannot be regarded as a universal requirement. One could hypothesize further, with less confidence to be sure, that there may not be *any* maternal influence after fertilization in any species.

Therefore, if our working hypothesis was that all the hereditary information must be contained in the gametes, we might expect that a detailed study of gametes and fertilization could shed light on inheritance. Whether or not this proved to be a rewarding approach, we would have to accept that any comprehensive theory of inheritance must be compatible with whatever was discovered about the behavior of gametes.

This second approach, cytology, was to make such astonishing progress in the last half of the 19th century that, five years before geneticists began to understand Mendel's work, E. B. Wilson was able to suggest that the nucleic acids were the physical basis of inheritance.

One might simplify these two research approaches for studying inheritance by saying that breeding sought to discover the process of inheritance and cytology sought to discover the substance of inheritance. The two approaches were to be combined in 1902–1903 by W. S. Sutton and, thereafter, the interplay of experimental breeding and cytology was to be the reason for the ensuing rapid and rewarding increase in our understanding of inheritance.

THE DISCOVERY OF CELLS: ROBERT HOOKE

The birthday of cytology can be fixed with considerable accuracy. On April 15, 1663 Robert Hooke (1635–1703) placed a piece of cork under his microscope and demonstrated its otherwise invisible structure to fellow members of the Royal Society of London.

The Royal Society had been started the previous year for the purpose of "Improving Natural Knowledge" (Birch, 1756–1757; Sprat, 1722; Thomson, 1812; Lyons, 1944; Stimson, 1949; Purver, 1967). It consisted of a few learned men of London who met on a regular basis, often weekly, to discuss scientific matters and how knowledge could be used to improve the useful arts. The inspiration for the formation of the Royal Society had come from an earlier suggestion of Francis Bacon.

Hooke, a polymath of exceptional ability (Gunther, 1930–1938; 'Espinasse, 1962) was a very active member of the Royal Society. It was the custom for members not only to hold discussions but also to perform experiments and provide demonstrations. There was great interest in the new microscope that Hooke had constructed. He let the members look at parts of a moss plant on April 8, 1663. On April 15 "Mr. Hooke shewed two microscopical schemes, one representing the pores of cork, cut both transverse and perpendicular . . ." (Birch, 1756–1757, vol. 1, p. 218).

That was the beginning of two centuries of observation and experimentation that were to establish the Cell Theory.

Hooke's various observations were assembled and published in 1665, under the auspices of the Royal Society, as *Micrographia*. This was the world's first comprehensive view of a previously invisible part of nature.

Hooke and the other members were much influenced by Bacon's ideas and the Preface of *Micrographia* has a long and interesting discussion of how the old philosophy must be avoided:

> The Science of Nature has already too long made only a work of the Brain and Fancy: It is now high time that it should return to the plainness and soundness of Observations on material and obvious things.

The reader was not to expect "any infallible Deductions or certainty of Axioms" from him and Hooke asks that the reader

> Whereever he finds that I have ventur'd at any small conjectures, at the causes of the things that I have observed, I beseech him to look upon them only as doubtful Problems, and uncertain ghesses, and not as unquestionable Conclusions, or matters of unconfutable Science . . . [and] I desire him, not absolutely to rely upon these observations of my eyes, if he finds them contradicted by future Ocular Experiments of sober and impartial Discoverers. (Preface)

Hooke described and illustrated many objects in *Micrographia*: head of a pin, many small insects and their parts, feathers, vinegar eels, parts of many plants, hair, moulds, paper, petrified wood, fish scales, silk, sand, snow flakes, urine, and, of course, that piece of cork (Fig. 2).

Hooke imagined that cork consisted of a number of parallel tubes with cross partitions,

> These pores, or cells, were not very deep, but consisted of a great many little Boxes, separated out of one continuous long pore, by certain *diaphragms*. (p. 113)

He observed similar structures in many other kinds of plants. It is generally thought that Hooke described those boxes as empty and let it go at that. Not at all:

> Several of those Vegetables, whil'st green, I have with my *Microscope*, plainly enough discover'd these Cells or Pores fill'd with juices . . . as I have also observed in green Wood all these long *Microscopical* pores which appear in Charcoal perfectly empty of anything but Air. (p. 116)

This discovery of cells in cork and other plants could have been of general importance or it could have been a minor feature of a few kinds of organisms. Continued research was to show that the bodies of plants consisted entirely or almost entirely of similar box-like structures and, in time, the concept was extended to animals. Hooke had made an interesting observation that was not important at the time—it became an important discovery because of later research.

And it took a very long time for it to become important even though many other investigators observed cells in plants. For example, a fellow member of the Royal Society, Nehemiah Grew (1641–1712), published a monograph in 1682 that contained many beautiful plates showing the microscopic structure of plants (Fig. 3).

It took more than two centuries for it to be realized that knowledge of cells was essential for an understanding of inheritance. We can be certain that when Robert Hooke sat down to his microscope he was not intending to unravel the mysteries of inheritance. There was no more reason to believe that cells had anything to do with inheritance than, for example, did the bristles he observed on the surface of a flea he described in such detail.

Time and time again in science it turns out that the explanations in one field come to depend on those already made in entirely different fields. And we must remember that the entire field of cytology was impossible until knowledge of optics and the grinding of lenses, plus a genius or two, were to make microscopes feasible.

THE CELL THEORY

Cells became truly important only when the hypothesis was proposed that the bodies of all organisms are composed solely of cells or the products of cells. That hypothesis was formulated and tested early in the 19th century and it is associated mainly with three observers: R. J. H. Dutrochet, Matthias Jacob Schleiden, and Theodor Schwann.

But how could one possibly prove that "the bodies of all organisms are composed solely of cells or the products of cells?"

Obſerv. XVIII. *Of the* Schematiſme *or* Texture *of* Cork, *and of the Cells and Pores of ſome other ſuch frothy Bodies.*

I Took a good clear piece of Cork, and with a Pen-knife ſharpen'd as keen as a Razor, I cut a piece of it off, and thereby left the ſurface of it exceeding ſmooth, then examining it very diligently with a *Microſcope*, me thought I could perceive it to appear a little porous; but I could not ſo plainly diſtinguiſh them, as to be ſure that they were pores, much leſs what Figure they were of: But judging from the lightneſs and yielding quality of the Cork, that certainly the texture could not be ſo curious, but that poſſibly, if I could uſe ſome further diligence, I might find it to be diſcernable with a *Microſcope*, I with the ſame ſharp Pen-knife, cut off from the former ſmooth ſurface an exceeding thin piece of it, and placing it on a black object Plate, becauſe it was it ſelf a white body, and caſting the light on it with a deep *plano-convex Glaſs*, I could exceeding plainly perceive it to be all perforated and porous, much like a Honey-comb, but that the pores of it were not regular; yet it was not unlike a Honey-comb in theſe particulars.

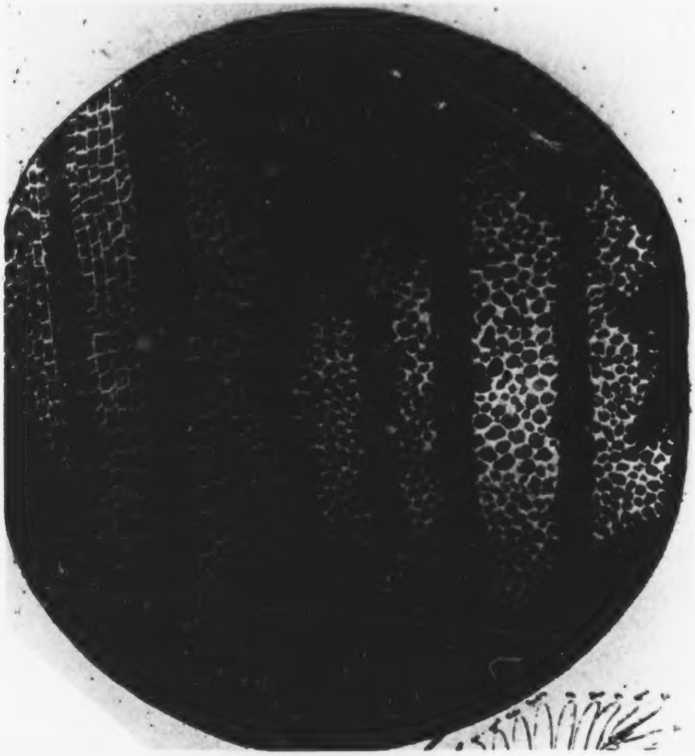


FIG. 2. Part of the text and the illustration from Robert Hooke's observations on cork. (Hooke, 1665)

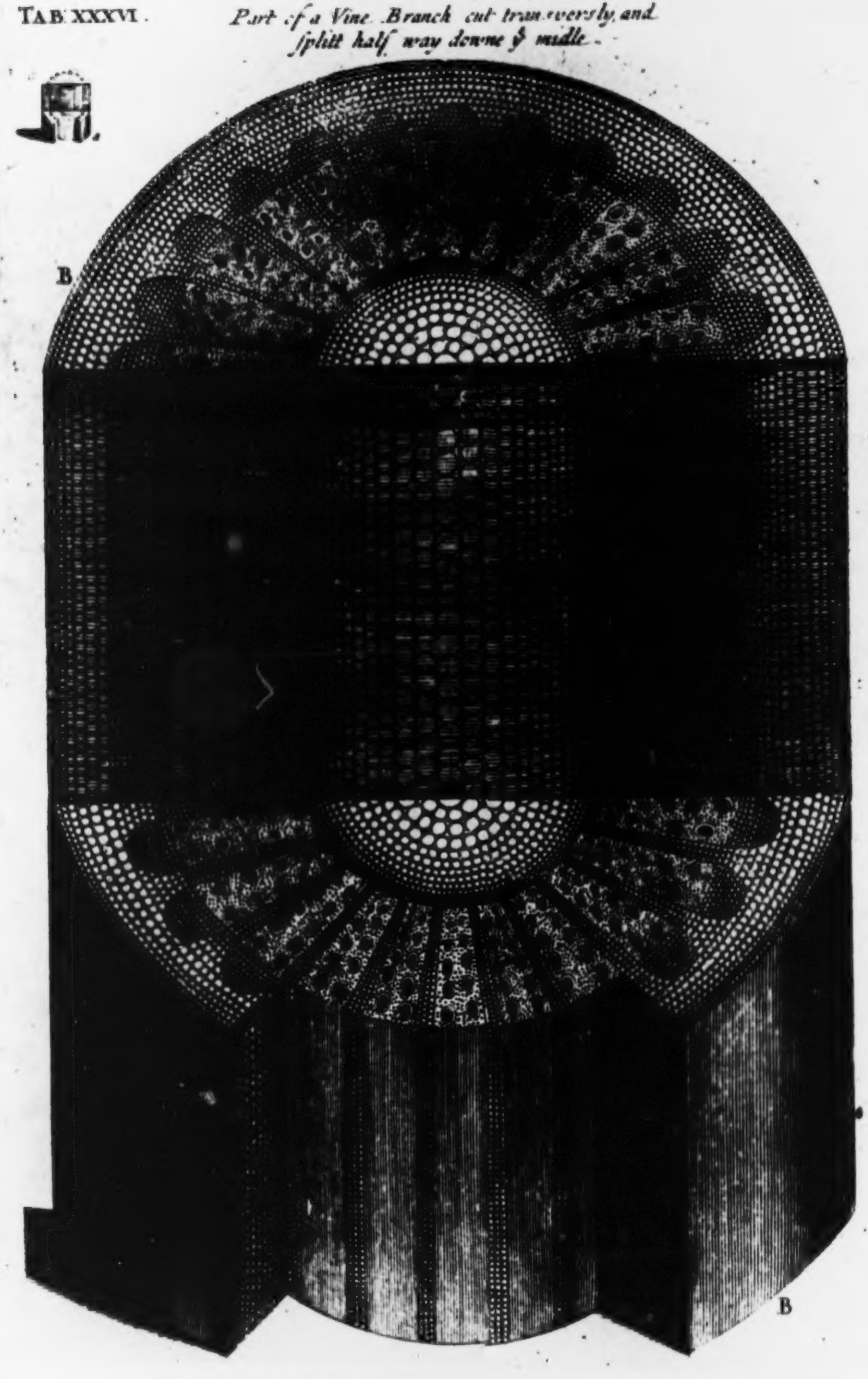

TAB: XXXVI.
Part of a Vine Branch cut transversly and splitt half way downe y midle.
B
B

FIG. 3. The cellular structure of a vine branch. (Grew, 1682)

That would be a profitable question for your students to consider. In doing so they would come to learn something important about scientific concepts.

The answer is, of course, that such a statement could not possibly be proven. How could one study all organisms? Most are long gone from this earth. How might your students evaluate this statement: "The bodies of dinosaurs were composed of cells"? It would not even be practical to study one individual of all living species. All that one can hope for in science is that a statement is "true beyond all reasonable doubt." Following Hooke's initial observations, it was found that cells were a common feature of plants. More and more individual plants and more and more species were studied and all were found to have those cell-like structures. It was observed that these microscopic structures were not all the box-shaped cells of cork. Cells were discovered to come in various shapes and sizes (Fig. 3). We must not forget that these early microscopists were not observing cells as we understand them today but cell walls.

SCHWANN AND CELLS IN ANIMALS

With few exceptions the bodies of animals contain no structures resembling the "cells", *i.e.*, the cell walls, of plants. Thus it required a great deal of study and bold imagination before it became obvious that the concept of cells could be profitably applied to animals. This was first accomplished mainly by Theodor Schwann (1810–1882) in his monograph of 1839, published when he was 29 years old. Some of the illustrations are reproduced in Figure 4. He emphasizes the great difference between the cells of plants and the structures in animals but suggested that they are fundamentally the same.

> Though the variety in the external structure of plants is great, their internal structure is very simple. This extraordinary range in form is due only to a variation in the fitting together of elementary structures which, indeed, are subject to modification but are essentially identical—that is, they are cells. The entire class of cellular plants is composed solely of cells which can readily be recognized as such; some of them are composed merely of a series of similar or even only of a single cell.
>
> Animals being subject to a much greater range of variation in their external form than is found in plants also show (especially in the higher species) a much greater range of structure in their different tissues. A muscle differs greatly from a nerve, the latter from a cellular tissue (which shares only its name with the cellular tissue of plants), or elastic tissue, or horny tissue, etc. [This paragraph will be continued after the following suggestion.]

WHY CALL ALL THESE DIVERSE STRUCTURES "CELLS"?

It would be most valuable to stop in the middle of Schwann's paragraph and ask your students to consider this problem. Show them the data: modern slides of various types of cells in plants and especially animals. How can it be useful to maintain that neurons, muscle, and tissues of kidney, lung, blood, cartilage, bone, intestine wall, etc., are made of the same sort of structures? When they are obviously so different, why maintain that they are fundamentally the same? And what is to be gained by claiming that these diverse structures in animals can be equated with the very different looking structures in plants?

BACK TO SCHWANN

Part of the answer emerges

> If, however, we go back to the development of these tissues, then it will appear that all of these many forms of tissue are constituted solely of cells that are quite analogous to plant cells . . . . The purpose of the present treatise is to prove the foregoing by observations.

That is, in spite of the great diversity of structures that Schwann proposed to call cells, all develop from simpler structures that could be compared more readily with the cells of plants.

The speculation of your students may have raised the problem of the need for a

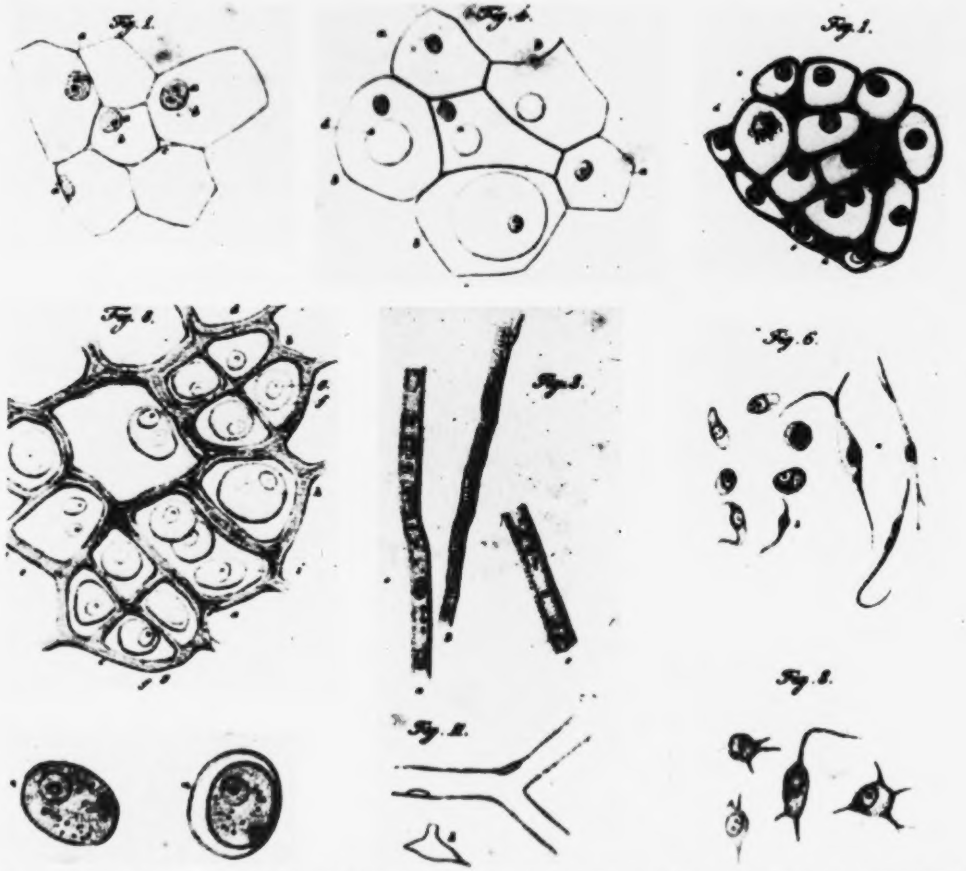


FIG. 4. Some of the illustrations from Schwann's monograph. Upper row, left to right: onion cells, notochord of a fish, cartilage of a frog. Middle row: cartilage of a tadpole, muscles of a fetal pig, areolar cells of a pig embryo. Bottom row: ganglion cells of a frog, capillary in a tadpole's tail, cells of a pig embryo. Note that nucleus and nucleoli are shown in nearly all cells. (Schwann, 1839)

way to define "cell." If neuron and leukocyte are both "cells," there must be a common basis for so classifying them. Schwann found a criterion, the presence of nuclei, that was more important than the origin of highly differentiated cells from simpler cells.

Only six years earlier, in 1833, Robert ("Brownian Motion") Brown (1773—1858) had described a single circular areola, or nucleus, in the cells of orchids and many other kinds of plants. Previous observers had noted these structures, illustrated them in their publications, but had attached no importance to them. Brown found that many kinds of cells contain nuclei but did not speculate on their significance.

Schwann then changed the rules for defining cells. Instead of relying on shape, which in plants meant the structure of the walls, he chose to base the definition on the presence of a nucleus.

> The most frequent and important basis for recognizing the existence of a cell is the presence or absence of the nucleus. Its sharp outline and its darker color make it easily recognizable in most cases

> and its characteristic shape, especially if it contains nucleoli . . . identify the structure as a cell nucleus and make it analogous with the nucleus of the young cells contained in cartilage and plant cells . . . . More than nine-tenths of the structures thought to be cells show such a nucleus and in many of these a distinct cell membrane can be made out and in most it is more or less distinct. Under these circumstances it is perhaps permissible to conclude that in those spheres where no cell membrane be distinguished, but where a nucleus characteristic of its position and form is encountered, that a cell membrane is actually present but invisible.

Although Schwann was a careful observer, his contribution was not primarily what he saw but how he interpreted the observations. Previous investigators had emphasized the boxes. Schwann emphasized what was *inside* the box. For him the animal cell became a bit of living substance containing a nucleus and bounded by a membrane and, in the case of plants, further encased in cell walls.

What does this new view of cells have to do with inheritance? Very little, one must admit. Two other bits of information are required before cells can be considered to have an important relation to inheritance: the discovery that the gametes are cells and the realization that cells originate only from other cells.

GAMETES AS CELLS

Schwann recognized that ova are cells since they exhibited the structure required by his definition of cells. The nature of spermatozoa was less clear. Even the name, meaning "sperm animals," indicates uncertainty. In 1667 Leeuwenhoek, or one of his students, had discovered and reported to the Royal Society of London that seminal fluid contained some microscopic creatures that were imagined to enter the egg and achieve fertilization. That hypothesis was hotly contested and some imagined that the spermatozoa were parasites. In the 12th edition of *Systema Naturae* (1766–1768), Linnaeus tentatively listed the spermatic animalcules of Leeuwenhoek but felt that the determination of their proper place in the system of classification must be left for later research (Dobell, 1960, p. 377).

A little more than a century later, in 1784, Spallanzani conducted some remarkable experiments to ascertain the function of semen in the reproduction of frogs. During breeding the males clasp the females and, as we now know, deposit sperm on the eggs as they leave the female's cloacal opening. This was not known to Spallanzani but he discovered it. Another investigator with whom he corresponded had attempted, without much success, to discover the role of male frogs by putting trousers on them. Now to Spallanzani:

> The idea of the breeches, however whimsical and ridiculous it may appear, did not displease me, and I resolved to put it in practice. The males, notwithstanding this incumbrance, seek the females with equal eagerness, and perform, as well as they can, the act of generation; but the event is such as may be expected: the eggs are never prolific [that is, they do not develop], for want of having been bedewed with semen, which sometimes may be seen in the breeches in the form of drops. That these drops are real seed, appeared clearly from the artificial fecundation that was obtained by means of them. (vol. 2, p. 12)

In another experiment he filtered semen and found that it lost its fertilizing power. He saw what we now call sperm but did not regard them as essential for reproduction.

> Having often observed the seminal liquor of the toad, I found it very full of spermatic worms, which, like those of the frog, have an oblong shape, and writhe their body as they move. Upon two occasions I have been greatly surprised at finding this fluid totally destitute of inhabitants. I was induced to try, whether it is also destitute of fecundating virtue, but I found that it was just as effectual in this respect, as that which most abounds with these diminutive animals. (vol. 2, p. 118)

It was not until 1854 that George Newport was able to offer good evidence, using frogs, that the sperm cells enter the egg at fertilization.

(Here and elsewhere it is often difficult to give credit for the scientist who discovered an important biological phenomenon. After all, the discoverer of sperm, Leeuwenhoek, had thought sperm were the agents of fertilization. Others antedating Newport had the same opinion but it was Newport who made the first convincing observations. And, as was noted before, microscopists had observed and published illustrations of cells with globules that were later identified as nuclei before Brown emphasized their importance.)

In 1841 Kölliker studied the histology of the testis and found that some of the testis cells are converted into sperm. Sperm are so unusual in appearance that they are not likely to be considered cells. However when they can be shown to be derived from typical cells, their true nature becomes apparent. Sperm, then, are to be regarded as highly modified cells.

This is how our analysis stands:

1. Gametes are the only physical link between generations, at least in many organisms and possibly all.
2. Therefore the gametes must contain all of the hereditary information.
3. Since ova and sperm are cells, all of the hereditary information must be contained in these sex cells. Therefore, the physical basis of inheritance is the sex cells.

This does *not* mean that all cells contain hereditary information. One could still imagine that the gametes are specialized cells into which the factors responsible for inheritance, gemmules perhaps, somehow enter. We still need that second bit of information: "What is the origin of cells?"

Omnis Cellula e Cellula?

Cell division had been observed in 1835 but it was not realized that this is a general phenomenon. Schwann (1839) had a very different notion about the origin of cells.

> The general principles in the formation of cells may be given as follows. At first there is a structureless substance which may be either quite liquid or more or less gelatinous. This, depending on its chemical constitution and degree of vitality, has the inherent ability to bring about the formation of cells. It seems that usually the nucleus is formed first and then the cell around it. Cell formation is in the organic world what crystallization represents in the inorganic world. The cell, once formed, grows through its inherent energy, but in doing so it is guided by the organism as a whole in the way that conforms to the general organization. This is the phenomenon basic to all animal and plant growth. It is applicable to cases where the young cells originate in the mother cell, as well as those where they are formed outside of them. In both instances the origin of cells occurs in a liquid or in a structureless substance. We call this substance, in which cells are formed, a cell germinative substance or Cytoblastema. It can be compared figuratively, but only figuratively, with a solution from which crystals are precipitated.

This hypothesis for the origin of cells holds that they are episodic events in the life cycle of organisms. If true, the unit of inheritance must be the entire organism, not the cell. Schwann's hypothesis for the origin of cells was soon rejected by his contemporaries, since cell division was observed repeatedly in a variety of organisms and in different periods of development. More and more investigators began to suspect that cell division was the sole mechanism for producing new cells.

This was an exceedingly difficult hypothesis to prove beyond all reasonable doubt. The microscopes and the techniques for studying cells in the early 1800s were most inadequate by later standards and it took many observations on different sorts of organisms and tissues before Rudolph Virchow was to express the view in 1855 that *omnis cellula e cellula* ("all cells from cells") and have it generally accepted. In a lecture given in 1858 (Virchow, 1863) he put it thus:

> A new cell can [never] build itself up out of any non-cellular substance. Where a cell arises, there a cell must have previ-

> ously existed (*omnis cellula e cellula*), just as an animal can spring only from an animal, a plant only from a plant. In this manner, although there are still a few spots in the body where absolute demonstration has not yet been afforded, the principle is nevertheless established, that in the whole series of living things, whether they be entire plants or animal organisms, or essential constituents of the same, an eternal law of *continuous development* prevails. There is no discontinuity of development of such a kind that a new generation can of itself give rise to a new series of developmental forms. (Virchow, 1863, Lecture II)

Of course not everyone agreed with Virchow that all cells and all organisms come from preexisting cells and organisms. Many observers continued to believe that cells could arise *de novo* and presented seemingly accurate observations to prove it. It was thought by some that whole organisms could arise *de novo* as well. Pasteur and the general acceptance that spontaneous generation cannot occur were still in the future. Nevertheless the twin hypotheses supported by Virchow were tested by more and more research and slowly it was established as true beyond all reasonable doubt that:

Omnis vivo e vivo
Omnis cellula e cellula

There was no question, then, that inheritance is based on cell continuity and we may now work with the hypothesis that all the hereditary information is contained not only in the germ cells but also, presumably, in the cells from which they arose—all the way back to the zygote. Also possible was the hypothesis that all cells contain the hereditary information necessary for the development of the individual and for its transmission, via the sex cells, to the next generation.

CYTOLOGY AND TECHNOLOGY

For most of human history we have relied almost entirely on our sense organs to tell us about the environment. Each sense organ detects only a narrow window in the range of possible stimuli. Our eyes, for example, can respond only to that portion of the electromagnetic spectrum between violet and red so we only see wavelengths between these two colors. Special instruments must be used if we are to detect the shorter ultraviolet, X-rays, and cosmic rays or the longer infra-red and radio waves.

Our unaided eyes fail also to tell us about objects that move very rapidly. The individual grey blades of a rapidly moving fan merge into a continuous circle that is less grey and the bullet leaving a rifle barrel is wholly invisible.

Nor can we see objects that are very small. The apparent uniformity of a half-tone illustration is a result of the individual dots of ink being too close together for the human eye to resolve. The twin headlights of an automobile appear as a single source of light when far away. As the automobile approaches, we become able to resolve the single light source into two.

Human eyes vary in their ability to resolve two objects, that is, to determine whether an object is single or multiple. The limit of resolution is about 100 microns at reading distance. Most individuals with normal eyes can distinguish two objects one millimeter apart at a distance of about 10 meters. (Should your students find this statement astonishing, suggest that they determine the value for their eyes.) A more general statement is that the human eye can resolve objects separated by an arc of 1 minute. That value was determined by Robert Hooke (1674) who wondered how far apart double stars had to be before they could be seen as two. When they were closer than 1 minute of arc, most people would see only a single point of light. Some people can do better and the maximum resolving power for the human eye is about 26 seconds of arc.

Nearly all cells are too small to be seen by the human eye so, obviously, cytology was not even theoretically possible before the invention of the microscope—probably in the 1590s. A long lag followed until 1663 when Hooke demonstrated those slices of cork to the members of the Royal Society. In fact, there was little serious and sustained work with microscopes before the

19th century. For most of their early history microscopes were little more than adult toys.

The small size of cells is not the only problem that makes studying them difficult. Most animals and their tissues are opaque and, since the compound microscope is most effective when objects are illuminated by transmitted light, the object to be studied must be either very thin or be sliced so thin that light can pass through. Imagine trying to cut liver into slices about 10 microns in thickness, which would be necessary to study the cells. Furthermore liver cells, consisting mostly of water, would soon dry out and be a shriveled mess. This is a special problem with animal cells, which lack the supporting walls of plant cells.

Very special methods had to be developed by the microscopists of the early 19th century if they were to learn about the cellular nature of organisms and, later on, the internal structure of cells themselves. It became common practice, therefore, to try to preserve tissues in such a manner that the cellular structure would remain intact and thin slices could be made.

The first step was fixation. This involved treating the material with alcohol, formaldehyde, or solutions of picric acid, potassium dichromate, mercuric chloride, or osmium tetroxide. These chemicals kill and harden cells, often by coagulating the proteins. It was hoped, of course, that this would be done in such a way that the parts of the cells would resemble the living state to an acceptable degree.

The fixed tissue could then be embedded in paraffin wax and slices made with a sharp razor or an instrument devised for this specific purpose—the microtome.

Even these thin slices might reveal very little. The cells and their internal structure might be indistinct. But the inventive microscopists tried everything and found that some dyes would stain some structures in cells but not others.

In 1858 Gerlach found that a dilute solution of carmine would stain the nucleus more intensely than the cytoplasm. This substance is derived from the dried bodies of female cochineal insects (*Coccus cacti*), which live on cactus plants in Central America and the southwestern United States.

In 1865 Böhmer found that hematoxylin, extracted from the logwood tree (*Haematoxylon campechianum*) of Central America, also had more affinity for the nucleus than the cytoplasm.

Later aniline dyes were manufactured in a vast variety for the textile industry and between 1875 and 1880 many were found to be useful in staining cells. One of these was eosin, which proved to have a great affinity for the cytoplasmic proteins. A common staining procedure was to use hematoxylin and eosin. This procedure stained the nucleus blue and the cytoplasm pink.

Similarly improvements were made in the last part of the 19th century in the microscopes available for cytological research. Many of these improvements were due to Ernst Abbe (1840–1905) and the Zeiss optical works in Jena, Germany. For most of his life Abbe was both professor of physics at the University in Jena and the principal lens designer for the Zeiss company and later its owner. In 1878 he developed his oil-immersion objective and, in 1886, the apochromatic objective. In the hands of a skilled microscopist magnifications of 2,500 diameters became possible. The light microscope was reaching the theoretical limit of its resolving power. This was a limitation due to the nature of light itself. That is, two objects can be resolved only if their distance apart is at least equal to half of the wavelength of light being used.

Although further opportunities for studying the fine structure of cells were to come with the phase-contrast and electron microscopes of the 20th century, we shall see that the cytologists of the last third of the 19th century were able to use the available technology to establish as highly probable the hypothesis that the physical basis of inheritance is the cell nucleus, or more specifically the chromosomes within it.

One must not imagine that these investigations involved no more than examining living or preserved cells with the best available optical equipment and describing as accurately as possible what was seen. The constant problem was whether or not a given structure in a prepared slide closely resembled the living state or whether it was an artifact resulting from the very drastic treatment to which cells were usually subjected. Consider the saga of a cell subjected to the following procedure by a cytologist of the late 1800s.

> Sections of vegetable tissues present a beautiful appearance under the microscope when doubly stained. They should first be soaked in alcohol, if green, to deprive them of chlorophyll, then subjected to a solution of chloride of lime (¼ ounce to a pint of water) until thoroughly bleached. Soak then in a solution of hyposulphite of soda (1 drachm to 4 ounces of water) for one hour, and after thoroughly washing in several changes of water transfer them to alcohol. Prepare some red staining fluid by dissolving ½ a grain of magenta crystals in 1 ounce of alcohol. Soak the specimen in this for thirty minutes, then rapidly rinse it in alcohol and place in a blue fluid made by dissolving ½ grain of anilin blue in 1 drachm of distilled water, adding 10 minims of dilute nitric acid and alcohol enough to make 2 ounces. Let the specimen remain only two or three minutes in this, rapidly rinse in alcohol, put in oil of cajeput, thence to turpentine, and mount in balsam. (Wythe, 1880, p. 348)

Apart from giving thanks to the Muses for the metric system, one may wonder how accurately the final preparation reflected the structure of living cells. The answer might be "Not very much" but if the treatment produced constant results it was often possible to interpret the living state from the preparations. Nevertheless, no important discovery in cytology in the 19th century was accepted when first proposed. Observations would be repeated and the original assertions would be confirmed by some and vehemently denied by others. An original erroneous report might cause many cytologists to spend months in attempting to repeat the observations.

There were endless debates about the fine structure of protoplasm since, it was assumed, one was looking at the very basis of life itself.

> Since the fundamental activities of protoplasm are everywhere of the same nature, investigators have naturally sought to discover a corresponding fundamental morphological organization common to all forms of protoplasm and underlying all its special modifications. (E. B. Wilson, 1900, p. 23)

Wilson then goes on to discuss the many hypotheses for the structure of protoplasm (pp. 23–30). Various cytologists had maintained that protoplasm was either granular, or a fibrous reticulum, or alveolar (composed of droplets) or some combination thereof.

The difficulties of interpreting structures seen under the microscope had been long understood as shown by this cautionary advice given by Henry Baker in 1742.

> Beware of determining and declaring your Opinion suddenly on any Object; for Imagination often gets the Start of Judgment, and makes People believe they see Things, which better Observations will convince them could not possibly be seen: therefore assert nothing till after repeated Experiments and Examinations in all Lights and in all Positions. When you employ the Microscope, shake off all Prejudice, nor harbour any favourite Opinions; for, if you do, 'tis not unlikely Fancy will betray you into Error, and make you think you see what you would wish to see. Remember that Truth alone is the Matter you are in search after; and if you have been mistaken, let not Vanity seduce you to persist in your Mistake. (p. 62)

Shades of Sir Francis Bacon and his Idols but still first-rate advice.

Cytology as a way of knowing, especially in the 19th century, reveals that science does not progress in an orderly fashion but by the constant testing and retesting of observations, experiments, and hypotheses. Far from being a straight line to truth the path was more like that reticulum some saw as the basic structure of protoplasm.

(We might add that the term "protoplasm" is rarely used today. Since it meant no more than "living substance," Hardin

[1956] suggested that we could do without it.)

REFERENCES TO MICROSCOPES AND CYTOLOGICAL PROCEDURES

R. M. Allen (1940), H. Baker (1742), J. R. Baker (1948–1955), Belling (1930), Blumberg *et al.* (1967), Bracegirdle (1978), Bradbury (1967, 1968), Bradbury and Turner (1967), Burrells (1977), G. Clark (1981), Clark and Kasten (1983), Conn (1928–1933, 1961), Gage (1925), Gatenby and Beams (1950), Hogg (1867), Nicolson (1956), Power (1664), Singer (1915), Slayter (1970), Spencer (1982), Woodruff (1939), and Wythe (1880).

Many additional references dealing with cytology before 1900 will be given at the end of this section.

WHAT'S IN CELLS?

During the last half of the 19th century, the hypothesis that the bodies of animals and plants are composed solely of cells and cell products was established as true beyond all reasonable doubt in the minds of most competent microscopists. We can speak, therefore, of the Cell Theory, using the term "theory" to apply to an entire body of data, hypotheses, and concepts relating to an important natural phenomenon.

To this day the Cell Theory remains the most important concept relating to the structure of animals and plants and in the 20th century it gradually became accepted as the most important concept relating to function as well.

It would be profitable for your students to suggest why the Cell Theory is such an important concept. Hopefully some will suggest that cells are the basic units of structure and function, that they are the smallest units capable of independent life, that is, they are able to use substances acquired from the environment to maintain and produce the living state. Cells are the least common denominator of life.

There was another important reason for studying cells: analysis at a simpler level of organization contributes to understanding at more complex levels. The interactions of chemical substances are better understood when we know their molecular structure. The movements of the human body can be studied at many levels. One may observe and describe the complex movements of a ballet dancer or baseball pitcher, beautiful and important in their own right. Understanding is increased when we obtain information about the many muscles and their attachments that make the movements possible. Other sorts of understanding come when we study muscles at the cellular level. And finally still more information is obtained when we learn about the activity of myosin, actin, and the other molecules involved in the movement of muscles.

Knowledge obtained at each level of organization contributes to an understanding of the total phenomenon, while each level retains its own validity. One cannot completely understand either a Waslaw Nijinsky or a Fernando Valenzuela merely by knowing about actin and myosin any more than one can predict the properties of water from knowing about hydrogen and oxygen.

Nevertheless, one does understand better more complex levels by knowing simpler levels. Thus it was thought inevitable that more would be learned about the living state by learning about cells. Those cytologists working after the publication of Darwin's *Variation* in 1868 must have wondered if they could discover the gemmules that formed the basis of the hypothesis of pangenesis. Would they see those postulated tiny hereditary granules in all cells?

Again it would be a profitable exercise for your students to play the role of a cytologist in the 1870s seeking the physical basis of inheritance. When they examined cells they would find all sorts of spheres, granules, and fibers. How could one establish whether or not any of these organelles had a role in inheritance? Or, in fact, how might one establish the function of *any* intracellular structure?

It is unlikely that your students will have any profound and useful suggestions—and neither did the cytologists of the time. They could do no more than undertake a program of random investigations of cells. This was a necessary stage in the development of the field of cytology—the identification of structures within cells and, where possible, learning something of their behavior. Seemingly cells from all available plants and animals were searched for examples of cell structures and one by one all the reagents from the chemical cabinet were dumped on cells and the consequences were observed—usually death of the cells. In cytology, then, this was the period of "Search and Destroy."

THE EPHEMERAL NUCLEUS

As noted before, the difficulty in studying living cells made fixed and stained preparations the favorite material. In such material the most prominent structure is Brown's nucleus. Many dyes, especially basic dyes such as carmine or hematoxylin, stain the nucleus heavily and this, together with its apparently universal presence suggested that it must be important.

But what is its origin? It took nearly a half century of observation and experiment by numerous cytologists to find out. In 1835 Valentin suggested that nuclei are formed by precipitation. Three years later Schleiden, followed by Schwann, also suggested a *de novo* origin. As late as the 1860s and 1870s some prominent cytologists continued to believe that at least some nuclei can have a non-nuclear origin.

Concurrently other equally competent cytologists were claiming that all nuclei originate from existing nuclei. Various methods were suggested—usually some form of pinching in two or fragmentation, a process that later came to be known as amitosis.

There was no necessary reason, of course, why there should be a single mechanism for the origin of nuclei. Considering the large amount of variability of natural phenomena, one should not be surprised if there were a variety of modes. Nevertheless, scientists seek the regularities in nature and it would be more intellectually satisfying if the concept of a constant mechanism of nuclear origin proved to be the case.

In retrospect we can see how even the most careful observation can lead to interpretations later shown to be incorrect. Thus, in what was considered favorable material—the early embryos of sea urchins—the nucleus appeared to pinch in half immediately before the cell as a whole divided. Figure 5 shows the first cell division and the beginning of the second in a sea urchin embryo. "Fig. 15" in this Figure 5 shows the zygote nucleus and in "Figs. 16–18" it forms a dumb-bell shaped object. In "Fig. 19" the egg has cleaved and each daughter cell has a nucleus. These drawings were published in 1876 by Oskar Hertwig. By that time he was aware that within the nucleus, which seemed to be dividing by amitosis, there were rods that could be seen after the eggs were fixed and stained.

There was another seemingly universal phenomenon that was difficult to explain for those maintaining that there is a fundamental type of continuity of the nucleus. The nucleus *does* disappear before the cell divides. That is, the spherical body that Brown and Schwann held to be a constant cell structure vanishes. In stained preparations it could be seen that, as the spherical nucleus vanishes, rod-shaped bodies not previously present made their appearance. Intensive study of these rods (later called chromosomes) led to the next major advances in cytology.

MITOSIS

In 1873 A. Schneider published what can now be taken as the first reasonable account of the complex nuclear changes, now called mitosis, that occurred at the time the cell divides. In the same year Otto Bütschli and Hermann Fol made similar reports.

Schneider's account was the most complete. His purpose was to describe the morphology of *Mesostoma*, one of the platyhelminths. Nearly all of his paper is devoted to the structure of this small flatworm but, being a careful observer, he described everything that he saw. Fertilization is internal in *Mesostoma* and early development takes place in the uterus. He provided illustrations of what he saw (Fig. 6).

The first drawing shows the egg surrounded by follicle cells. In the very center is the small nucleus with its even smaller nucleolus. The spiral structures are sperm. The egg is the clear central area of the illustration and the much smaller globular structures surrounding it are the follicle cells, which are omitted in the succeeding drawings. Shortly before the cell divides the outline of the nucleus becomes indistinct. Schneider found, however, that by adding a little acetic acid it becomes visible, though folded and wrinkled. Later the nucleolus disappears and all that remained of the nucleus was a clear area in the cell. However, acetic acid treatment revealed a mass of delicate, curved fibers. The second drawing shows these strands, the chromosomes (a term not to be introduced until 1888), lined up on an equatorial plate. The strands seem to become more numerous, and when the cell divides they pass to the daughter cells.

What was one to make of this observation? The answer was far from clear. If one could not see the strands in the living cells and, if they appeared suddenly when acetic acid was added, would it not be reasonable to assume they were artifacts? Nevertheless, the fact that strands were observed repeatedly, and that they seemed to undertake these strange movements, argued that they might be present, though invisible, in the living state.

There is no evidence that Schneider realized he was giving a reasonably accurate first description of a process that was soon recognized to be of tremendous importance. His primary concern was the morphology of *Mesostoma* and to use the data obtained to ascertain the relation of these little animals to other invertebrates. In these post-Darwinian years one of the main preoccupations of biologists was to use morphology to try to sketch the broad outlines of organic evolution.

The events in cell division, and especially the changes in the nucleus, were immediately recognized as important phenomena to be studied. In fact, they seemed to be about the only constant changes that occurred in cells.

In 1881 Professor Mark of Harvard University published a comprehensive review of cell division. In his extensive bibliography there are 194 papers by 86 authors that were published between 1874 and 1878 alone. That is, in the five years immediately after the first reports of Schneider, Bütschli, and Fol. This was a period of more or less blind experimentation. The animal and plant kingdoms were combed for favorable material, which was studied while living as well as after various sorts of fixation and staining. There were few generally accepted conclusions. The persistent bugaboo of cytology—is it real or is it an artifact?—made progress slow and tentative.

Chromosomes *were* artifacts in most materials, that is, they could not be seen in living cells and became obvious only after the most drastic treatment. Their very name, meaning colored body, indicates their artifactual nature—no one maintained that the living cell possessed any colored rod-like structures. It could be, however, that such structures are present, though invisible, in the living cell and they could be made visible by appropriate techniques. The human eye, aided by the crude microscopes of the day, might not be able to "see" all of the cellular structures present.

What was necessary was to find material in which a direct comparison could be made between the structures of living cells and the same structures after fixation and staining. Could it be shown that the readily observed structures of fixed and stained cells closely resembled the difficult-to-see structures of living cells? If so, one could use fixed and stained preparations with the assurance that they reflected the living state and one could establish the degree of resemblance.

That was the accomplishment of Walther Flemming.

WALTHER FLEMMING

Flemming was successful in determining that the nuclear events observed in cell division in fixed and stained material have their counterparts in living cells. Although he did not discover mitosis, we owe to him more than to anyone else the concept of mitosis that we hold today. Only details were added after Flemming. His success was due to the material he selected for study, in being careful to check in living cells the things observed in fixed and

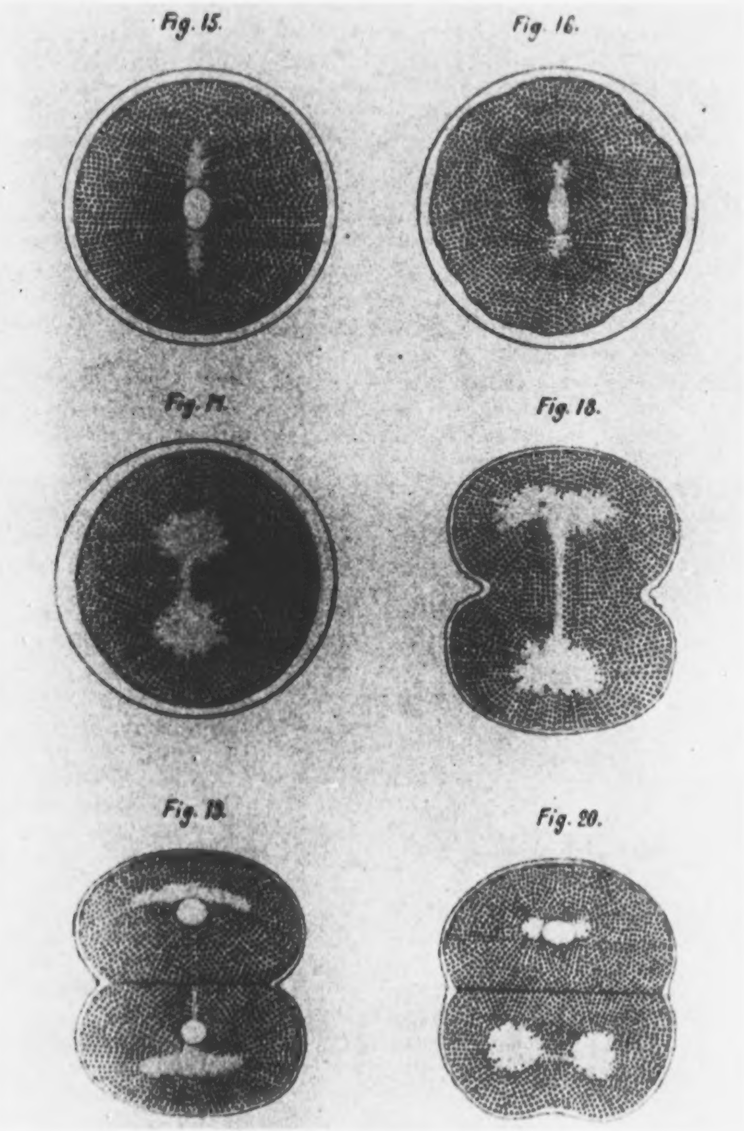
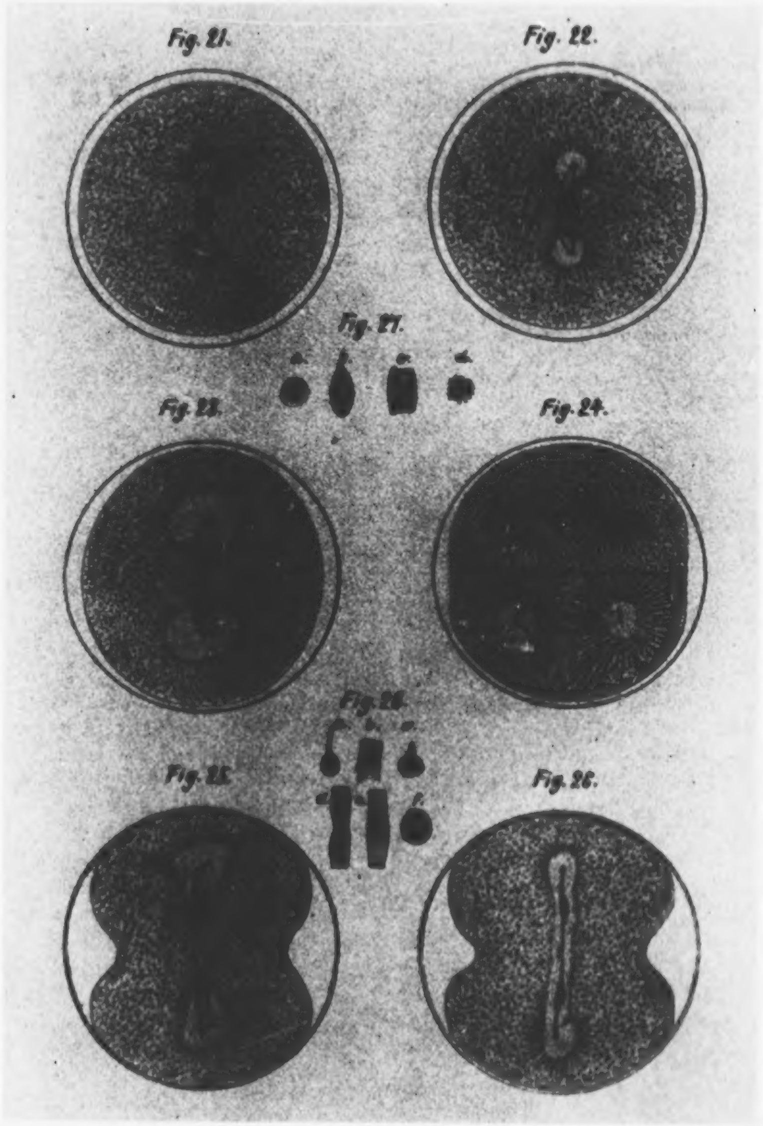


Fig. 15.
Fig. 16.
Fig. 17.
Fig. 18.
Fig. 19.
Fig. 20.

FIG. 5. Cell division in a sea urchin embryo. Hertwig's Figures 15–20 show what can be seen in living embryos. The nucleus appears to pinch in two. In the living embryo it is simple to determine the sequence of events. Shown are embryos at various times after fertilization: 30 minutes (Fig. 15), 45 minutes (Fig. 16), showing the two division centers, 60 minutes (Fig. 17), 65 minutes (Fig. 18), 70 minutes (Fig. 19). Figure 20 shows the beginning of the next division. Figures 21–26 show what can be seen after the embryos have been

stained cells, and in being able to use microscopes that were very much better than any available previously.

Not only does the use of living cells give one greater confidence that what is being observed is real, not artifact, but it also allows one to determine the sequence of events. This can be brought home to stu-



fixed in osmic acid and stained with carmine. The chromosomes, spindles, centrosomes, and asters have now become visible. The figures, in times after fertilization, are: 40 minutes (Fig. 21), 45 minutes (Fig. 22), 60 minutes (Fig. 23), second cleavage (Fig. 24), 65 minutes (Figs. 25, 26). (Hertwig, 1876) (Compare the rather vague rendition of the sea urchin chromosomes with Flemming's illustrations of amphibians in Fig. 7.)

dents by asking them to try to determine the sequence of mitotic events by studying the standard slides of onion root. Can one make an equally valid case for two nuclei fusing to form one as for one nucleus giving rise to two?

Early developmental stages provide a way to determine the sequence of nuclear

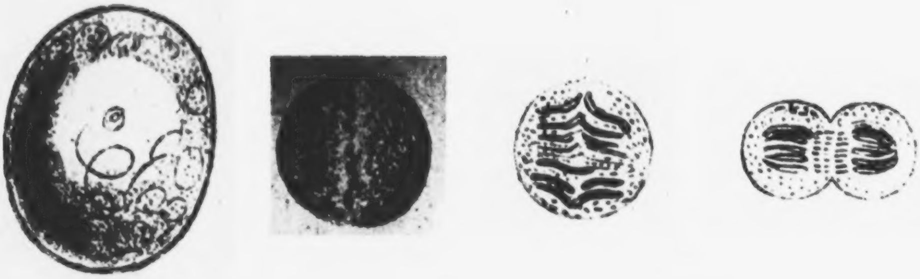


FIG. 6. Schneider's illustrations of the nuclear changes during cleavage in *Mesostoma* embryos. The left figure is of an uncleaved ovum (clear area with a nucleus and nucleous surrounded by follicle cells. The spiral structures are sperm). The other figures show the "strands," now chromosomes, and their movements during cell division. (Schneider, 1873)

changes—even in preserved cells. In fertilized echinoderm eggs, for example, cell divisions occur every half hour or so (depending on the temperature), and of greater importance, all the embryos develop synchronously. Thus, if small samples are preserved every few minutes and stained and studied later, one can be sure of the sequence of events. Embryos have rapid cell divisions—clearly a great advantage if one wishes to study the process. In most adult tissues a dividing cell is seen infrequently—except where there is rapid replacement or growth.

Flemming examined many sorts of cells and found that those in the epidermis of salamander embryos were worth detailed study. The chromosomes are huge by microscopic standards but, of much greater importance, with careful observation they can be seen in living cells. Figures 7 and 8 (from Flemming, 1882) show what he saw in living and preserved cells.

A nucleus not undergoing mitosis is said to be in the *resting stage*. This is an unfortunate term since it implies inactivity and it is now realized that great physiological activity is occurring during this stage. Flemming saw no chromosomes in the resting stage nuclei of living cells. The nucleus appeared to lack all internal structure. When such cells were fixed and stained the nucleus was seen to contain a dense and deeply staining network together with one or two large spherical granules, the nucleoli.

Changes in the nucleus are the first indications that mitosis is under way. In the apparently structureless living nucleus long delicate threads make their appearance. When they can first be seen, that is the start of *prophase*. (Mitosis is a continuous process that, for descriptive purposes, was divided into discrete stages by cytologists.) These threads condense into chromosomes that assemble in the middle of the cell at *metaphase*, at which time the nuclear membrane disappears. In stained cells the chromosomes were seen to be in an elongate fibrous structure—the spindle. Stained cells also revealed the presence of tiny granules, the centrioles, at the ends of the spindle. They also revealed another set of fibers, the astral rays, that radiate from the centrioles. In living cells during *anaphase* the chromosomes separate into two groups and move within the spindle area to opposite parts of the cell. When the chromosomes have reached the ends of the spindle, that is *telophase*. The chromosomes in living cells become less and less distinct and the nuclear membrane reforms. The nucleus is, once again, in the *resting stage*.

What is one to conclude about this process? Again, this might be a question for the class to consider.

It is obvious that *all* cell structures must be reproduced if the daughter cells are to be essentially identical with the parent cell. Flemming was able to explain how this is accomplished for chromosomes. If the chromosomes of a single cell are to be divided equally between the daughter cells, the chromosomes must double in number at some stage in the cell cycle. Flemming observed that when the chromosomes first appear in early prophase they are double so, sometime between their disappearance in the previous telophase and their reappearance in prophase, each chromosome must have doubled (Figs. 7, 8).

Today, of course, we consider chromosomes to be permanent cell structures even though they are readily visible only during mitosis. We also recognize the individuality of chromosomes, that is, they usually exist in homologous pairs with each pair containing a specific set of genes. Could any of this be concluded from the observations of Flemming? Not really. In fact, could the following hypothesis be denied? We will assume, with Darwin, that inheritance and the functioning of cells are due to specific gemmules. The gemmules are widely distributed during the resting stage when they are, presumably, directing the activities of the cells. Before the start of mitosis the gemmules congregate in the nucleus and join one another, like beads on a string, to form long strands—the chromosomes. The gemmule-bearing chromosomes are then divided in mitosis and each daughter cell receives an allotment. The chromosomes then break down and the gemmules are dispersed throughout the cell, where they carry out their directing activities. Will Flemming's data support or deny this hypothesis?

Those students who already know that genes are parts of chromosomes may suggest that Flemming's observations suggest strongly that chromosomes are involved in inheritance. The argument may go something like this: since the mitotic process ensures that each daughter cell receives its allotment of chromosomes this must indicate, beyond much doubt, that such an elaborate and precise mechanism for duplication and distribution is of fundamental importance. And what can be more important than ensuring that the elements controlling inheritance and the life of each cell reach each cell?

But one might respond that, since the daughter cells come to be essentially identical with the parent cell, *all* cell products are reproduced. One might argue that it is merely an accident that the process of reproduction and distribution is more readily visible for the chromosomes. There is no reason, therefore, not to assume that chromosomes, cell membranes, and all those granules and globules in the cytoplasm have an equal chance of being involved in inheritance.

Those students who already know the outcome should be asked to suggest what sorts of cytological observations and experiments are required to show that chromosomes have individuality and permanence.

BUT MITOSIS CANNOT BE UNIVERSAL

Flemming and many other contemporary cytologists were making a strong case that mitotic divisions of the nucleus are a concomitant of cell division. This is a general statement that was based on putting together many observations on cells of numerous species of plants and animals. You might cite this to your students as an example of induction.

We can now use this general statement as a hypothesis to be tested. That is, we can switch to deductive reasoning. For example: if the hypothesis that the nucleus always divides by mitosis is true, then in each succeeding generation the number of chromosomes should double. This is inevitable, for if the nuclei of egg cells and sperm cells have been formed by mitosis, and if they unite in fertilization, the zygotes must have twice the number of chromosomes as the parents.

Yet they do not: Flemming and other cytologists were aware that the number of chromosomes seems to be about the same in all individuals and in all available generations of a species.

Obviously there is a problem with this hypothesis. There must be some mechanism for reducing the number of chro-

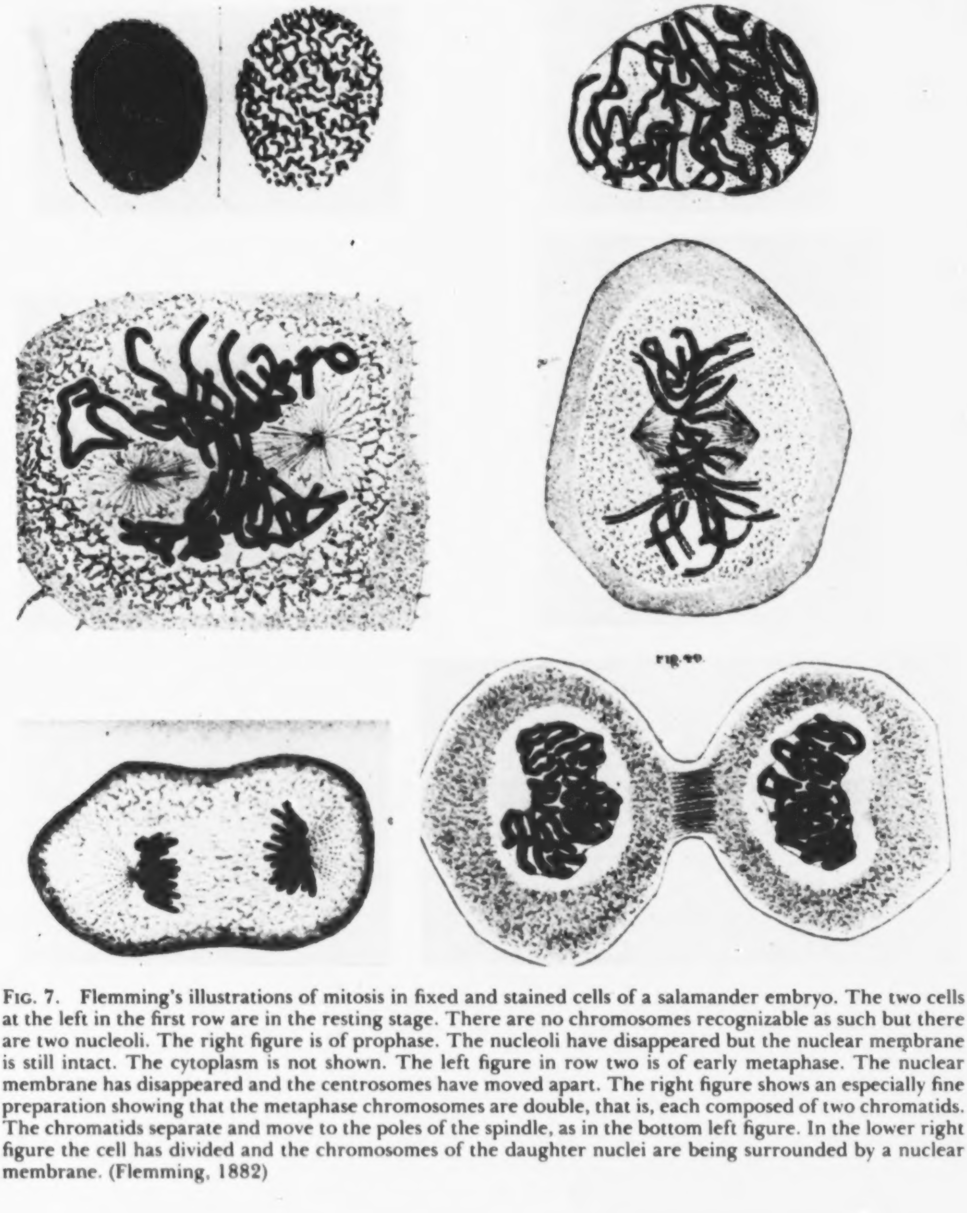


FIG. 7. Flemming's illustrations of mitosis in fixed and stained cells of a salamander embryo. The two cells at the left in the first row are in the resting stage. There are no chromosomes recognizable as such but there are two nucleoli. The right figure is of prophase. The nucleoli have disappeared but the nuclear membrane is still intact. The cytoplasm is not shown. The left figure in row two is of early metaphase. The nuclear membrane has disappeared and the centrosomes have moved apart. The right figure shows an especially fine preparation showing that the metaphase chromosomes are double, that is, each composed of two chromatids. The chromatids separate and move to the poles of the spindle, as in the bottom left figure. In the lower right figure the cell has divided and the chromosomes of the daughter nuclei are being surrounded by a nuclear membrane. (Flemming, 1882)

mosomes at or before fertilization. One might imagine that, when egg and sperm nuclei fused at fertilization, the chromosomes fused to one another or that half are destroyed. Or possibly there were some changes in chromosome number when the eggs and sperms were formed in the gonads.

THE SIGNIFICANCE OF POLAR BODIES

Various observers had noticed that, around the time of fertilization in the eggs of many species, tiny spheres were pinched off at the animal pole of the egg. They soon disappeared and, since no function was readily apparent, the non-committal term

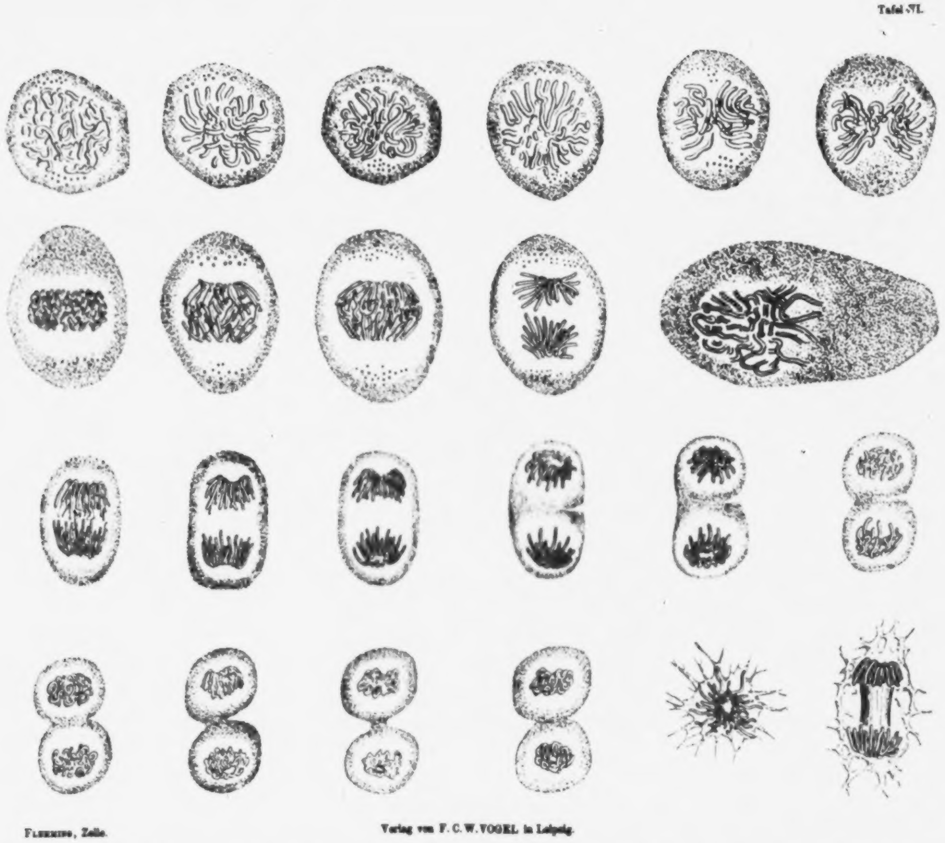

Tafel VI.
Flemming, Zelle.
Verlag von F. C. W. VOGEL in Leipzig.

FIG. 8. Flemming's illustrations of mitosis in the living cells of a salamander larvæ. The drawings are arranged in sequence beginning with prophase at the upper left and ending with two cells in the lower row. The last two figures show a polar view of chromosomes and a side view of telophase. The rightmost figure in row two shows that the chromosomes are double. (Flemming, 1882)

"polar bodies" was assigned to them. It was observed that in parthenogenesis a single polar body is formed but in fertilized eggs there always seem to be two. In some species one was formed before fertilization and a second after the sperm had entered. In other species two were formed after fertilization.

In 1887 August Weismann (reprinted in Weismann, 1889) proposed a hypothesis to account for the constancy of the amount of the hereditary material from generation to generation. On the basis of the observation of many cytologists,

> at least one certain result follows, viz. that there is an hereditary substance, a material bearer of hereditary tendencies, and that this substance is contained in the nucleus of the germ-cells, and in that part of it which forms the nuclear thread [some cytologists thought that the chromosomes formed a continuous thread or spireme in the resting stage], which at certain periods appears in the form of loops or rods [these are the chromosomes of mitotic stages]. We may further maintain that fertilization consists in the fact that an equal number of loops from either parent are placed side by side, and that the segmentation nucleus is composed in this way. It is of no impor-

> tance, as far as this question is concerned, whether the loops of the two parents coalesce sooner or later, or whether they remain separate. The only essential conclusion demanded by our hypothesis is that there should be complete or approximate equality between the quantities of hereditary substance derived from either parent. If then the germ-cells of the offspring contain the united germ-plasms of both parents, it follows that such cells can only contain half as much paternal germ-plasm as was contained in the germ-cells of the father, and half as much maternal germ-plasm as was contained in the germ cells of the mother. (pp. 355–356)

Weismann believed that the halving of the hereditary material of the mother demanded by his hypothesis occurred when the second polar body was formed.

> My opinion of the significance of the second polar body is shortly this,—a reduction of the germ-plasm is brought about by its formation, a reduction not only in quantity, but above all in the complexity of its constitution. By means of the second nuclear division the excessive accumulation of different kinds of hereditary tendencies or germ-plasms is prevented, which without it would be necessarily produced by fertilization. With the nucleus of the second polar body as many different kinds of idioplasm [a term for the hereditary material] are removed from the egg as will be afterward introduced by the sperm-nucleus; thus the second division of the egg-nucleus serves to keep constant the number of different kinds of idioplasm, of which the germ-plasm is composed during the course of generations. (p. 355)

And, if constancy is to be maintained from generation to generation, he argued a similar process must occur in the male.

> If the number of ancestral germ-plasms contained in the nucleus of the egg-cell destined for fertilization must be reduced by one half, there can be no doubt that a similar reduction must also take place, at some time and by some means, in the germ-plasms of the male germ-cells. (p. 370)

At the time these astonishing predictions were made, astonishing because ultimately they proved to be essentially correct, cytologists were finding evidence that supported them. The most important observations were being made on the nematode worm, *Ascaris*, which had the great advantage of having chromosomes that were few in number and large in size, making them relatively easy to study. By way of contrast, the echinoderm embryos had numerous small chromosomes that appeared identical and conveyed no suggestion of individuality or even exact constancy of number.

MEIOSIS IN THE *ASCARIS* FEMALE

In the 1880s major contributions were made to our understanding of gamete formation and fertilization. Three cytologists deserve special mention: Edouard van Beneden (1846–1912), Theodor Boveri (1862–1915), and Oskar Hertwig (1849–1922).

They discovered that there are two unusual cell divisions during the formation of gametes that result in the chromosome number being reduced by half—as Weismann said must happen. These two divisions are highly modified mitotic divisions and were given the name meiotic divisions—the names being so similar that they remain a problem for students to this day. In the descriptions that follow, the modern terminology will be used.

The ovary of *Ascaris* begins to form early in development and the huge increase in the number of its cells is a consequence of mitotic divisions. Each nucleus has four chromosomes, the diploid number, and before each division each chromosome is seen to have doubled by early prophase, forming the two chromatids. The eight chromatids are divided between the two daughter cells and the result is four chromosomes in each.

As the *Ascaris* female matures her ovary comes to contain enlarged cells, the ova, still with the diploid number of chromosomes. The ovum remains diploid until it has been released from the ovary and

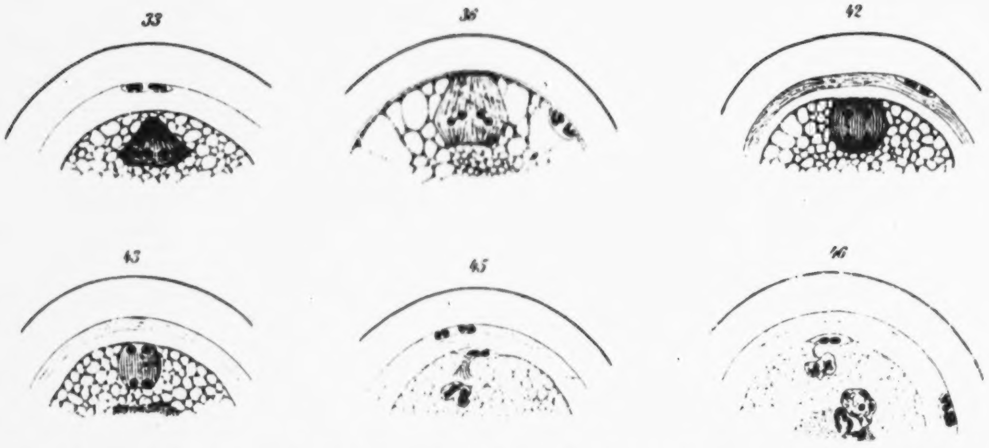


FIG. 9. Boveri's illustrations of meiosis is an *Ascaris* female. Previous to the figures shown here the four chromosomes had synapsed and replicated to form two tetrads. These were separated at the first meiotic division and two dyads went into the first polar body and two remained in the eggs. This is shown in Boveri's Figure 33. In Figure 36 the dyads are rotating prior to their separation in the second meiotic division. The second polar body is shown at 2 o'clock. Figures 42 and 43 show the dyads separating. In Figure 45 the second division is complete and the second polar body with its two chromosomes appear at the surface of the egg. The first polar body as above it. The two chromosomes in the egg are about to form the female pronucleus. Figure 46 shows the first polar body at 3 o'clock, the second polar body at the egg surface at 12 o'clock, the female pronucleus immediately below it, and the male pronucleus with the division apparatus at the bottom. (Boveri, 1887)

entered by a sperm. It is only then that meiosis begins and polar bodies are formed. Figure 9 from Boveri (1887) shows what happens.

At the onset of meiosis each of the four long chromosomes of the ovum shortens to form a tiny sphere. These four chromosomes then come together in pairs, a process known as synapsis. Then each chromosome is duplicated. Thus the cell will have two groups of four chromosomes each. Each group of four is known as a tetrad. The tetrads are divided by a highly unequal cell division that results in a small first polar body and a large egg cell. Each contains the diploid number of four chromosomes. These four chromosomes are not separate—they are in pairs. Thus, each tetrad has been divided into two dyads.

At the second meiotic division one observes a key feature of meiosis. The chromosomes are not duplicated. Thus each dyad enters the spindle and, at anaphase, its two chromosomes go to opposite poles and the cell divides unequally again. The result is a tiny second polar body with two chromosomes and a large ovum also with two chromosomes.

Thus meiosis in the female has, in two divisions, reduced the diploid number of four chromosomes to the monoploid number of two chromosomes. Weismann's hypothesis proved true, at least for the *Ascaris* female.

MEIOSIS IN THE *ASCARIS* MALE

Weismann's prediction for the male was found to be correct as well. When the testis was studied it was found that during early development its cells increase in number by mitotic divisions, that is, each son cell has the diploid number of four chromosomes (Bauer, 1893).

However, in the mature testis, the last two divisions before the cells differentiate into sperm are different. This is when the meiotic divisions occur in the male. As far as the chromosomes are concerned, the events are the same as in the female, but not so for the cell as a whole. Again the four chromosomes join in pairs, duplicate, and form the two tetrads. At the first meiotic division each tetrad is divided, a dyad going to each pole. In contrast with the first meiotic division in the female, two cells of equal size are produced. At the second meiotic division there is no chromosomal replication and the dyads are divided, each son cell ending with two chromosomes.

Thus one original diploid cell, with four chromosomes, will form four cells after the two divisions—each with two chromosomes, the monoploid number. There are no further divisions of these cells and each differentiates into a sperm cell (Fig. 12).

An essential difference between meiosis and mitosis is this: in mitosis there is one duplication of each individual chromosome for each cell division; in meiosis there is only one duplication of each chromosome for the two subsequent divisions. Thus, mitosis is a mechanism for maintaining constancy of chromosomal number in cell division whereas meiosis is a mechanism for halving that number.

FERTILIZATION

The basic fact of fertilization, namely that a sperm rather than the seminal fluid is required to initiate development of the ovum, was discovered by J. L. Prévost and J. B. Dumas in 1824. However the actual role of the sperm was not established by their work. As noted before, George Newport (1854) proved that the sperm penetrate the ova of frogs. But what happens then?

The answer came from the observations of Oskar Hertwig (1876). He noted, as had others before him, that shortly after fertilization the ova of sea urchins appear to have two nuclei (Fig. 10). One of these first appears just under the surface of the ovum. Hertwig suggested that this was derived from the sperm. The other nucleus was near the center of the ovum. Hertwig suggested that it was the female nucleus. Five minutes after fertilization the putative sperm nucleus moved inward toward the center of the cell. By 10 minutes after fertilization the two nuclei were side by side in the center of the ovum. By 15 minutes there was a single nucleus.

Hertwig believed that he was observing the essential feature of fertilization: the union of paternal pronucleus formed from the sperm with a maternal pronucleus in the ovum. That union produces the zygote nucleus that would, by mitotic cell divisions, produce the cells of the new individual.

Ascaris provided much better material for studying the details of fertilization, again because of its few large chromosomes. Van Beneden and Boveri described the process in detail. Figure 11 is from Boveri (1888).

The first illustration, *a*, is of an entire ovum shortly after the sperm has entered. The paternal pronucleus is in the lower right-hand quadrant. The two darkly stained irregular masses are the two chromosomes—two is the monoploid number. The structure forming the wrinkled cap immediately above the paternal pronucleus is the acrosome, which is the portion of the sperm head composed of Golgi material. The dark granular mass in the center of the ovum is the centrosome. It, too, originated from the sperm. There are four black bodies near 12 o'clock. The upper two are the chromosomes of the second polar body. The lower two are the monoploid number of chromosomes of the maternal pronucleus. The second polar body is shown in the sectioned embryos of *b*, *c*, and *e* as well. Do your students understand why only some of the sections show the polar body?

In *b* the maternal and paternal pronuclei have moved closer to one another and their chromosomes have become indistinct. In *c* the chromosomes have elongated greatly and, although we now know there are only two in each pronucleus, this cannot be told from the illustration (this is a vivid example of the great difficulty cytologists had in coming to the realization that the chromosomes of any one species are constant in number and are individually unique—much of the time they seemed to be as confusing as spaghetti). One can distinguish two dark granules in the centrosome. These are the centrioles.

In *d* the chromosomes have become distinct once again (from *b* through *c* they were going through a modified resting stage) and each pronucleus shows two. The

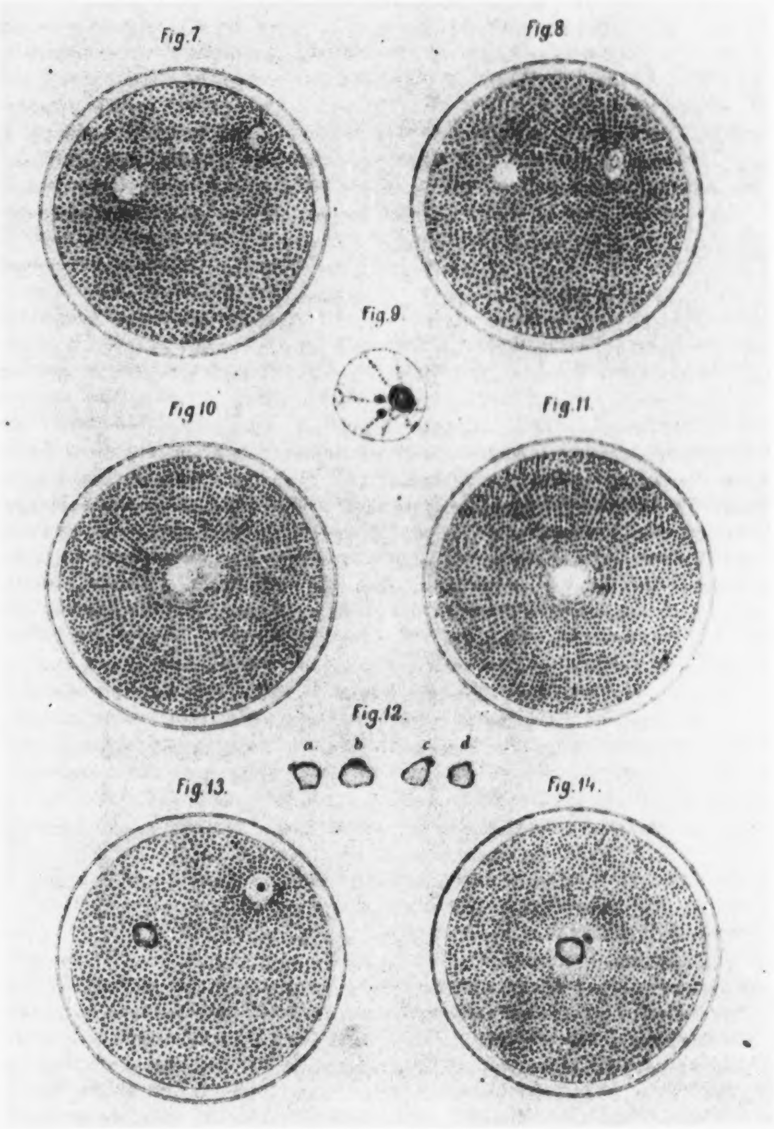


FIG. 10. Hertwig's illustrations of fertilization in the sea urchin. Figures 7, 8 (9 is of a mouse), 10 and 11 are of living embryos. His Figures 7 and 8 are 5 minutes after eggs and sperm were mixed. The female pronucleus is the clear area to the left and the male pronucleus is at the right. At 10 minutes (Fig. 10) the two pronuclei have come together in the center of the egg. At 15 minutes (Fig. 11) they appear to be completely fused. Figures 13 and 14 are of embryos fixed in osmic acid and stained with carmine 5 and 10 minutes, respectively, after the gametes were mixed. (Hertwig, 1876)

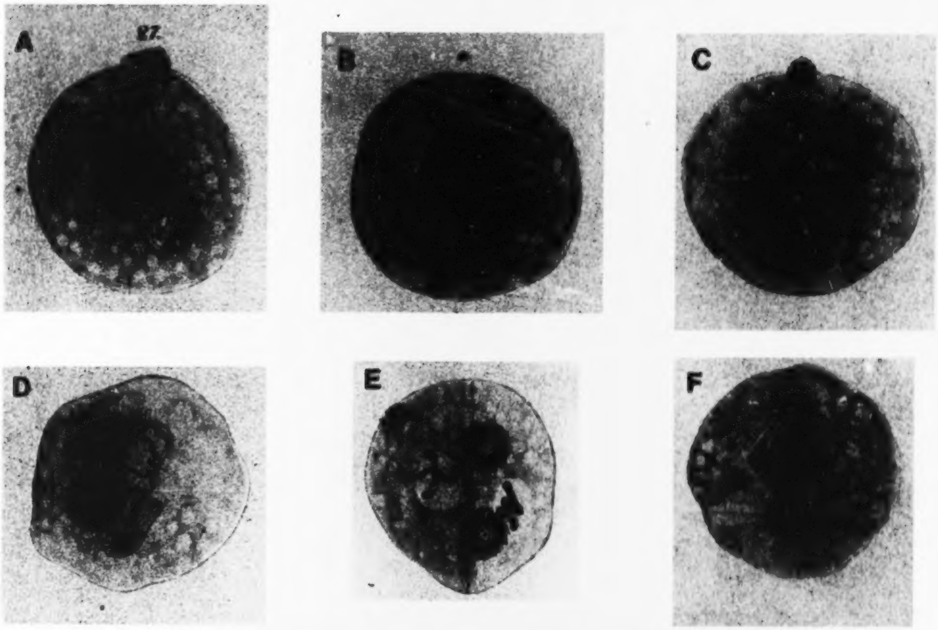


FIG. 11. Boveri's illustrations of fertilization in *Ascaris*. See text for details. (Boveri, 1888)

centrosome has divided in two, each with a centriole in the center. This process continues through *e*. In *f* four chromosomes, two from each pronucleus, are lined up on the spindle and shortly thereafter each is seen to be double, that is, be composed of two chromatids. The chromatids will separate to form independent chromosomes and one will go to each pole.

The form of the mitotic apparatus is shown well in *f*. At each end of the spindle one finds the tiny centriole, surrounded by a dark granular area—the centrosome. In preserved material fibers are seen to radiate from each centrosome, forming an aster. Other fibers extend from one centrosome to the other, forming the spindle. In *f* the cell is in metaphase of the first embryonic division and the chromosomes are lined up in an equatorial plate.

SIGNIFICANCE OF GAMETE FORMATION AND FERTILIZATION

It all turned out just as Weismann thought it must. The cells that were, many cell generations later, to form the gametes in both ovary and testis of *Ascaris* started out with four chromosomes, the diploid number. These cells divided repeatedly, always by mitosis.

In males the last two divisions of the sperm-forming cells of the testis, however, were meiotic, not mitotic. During these two divisions the cells divided twice but the chromosomes replicated only once. Each cell division was equal, that is, two cells of the same overall size were formed by each division (Fig. 12). This resulted in four cells of equal size, each with two chromosomes, the monoploid number. The four cells then differentiate into spermatozoa.

After many cell cycles of mitotic divisions, some of the ovarian cells enlarged greatly—forming the ova. As in the case with males, there were two meiotic divisions of the nuclear material with only a single replication of chromosomes. The first division of the cell was so unequal that most of the material remained in the cell that was to form the ovum and only a minute amount was included in the first polar body. This was repeated at the second division, which produced the tiny second polar body and the large ovum. Nevertheless, the nuclei of the second polar body and of the ovum were identical—each with the monoploid number of two chromosomes.

Meiosis in *Ascaris* therefore produced monoploid sperm and monoploid ova. The union of one of each was the origin of the diploid zygote—the beginning of a fine new nematode worm. The processes are summarized in Figure 12.

It was clear from the work of van Benedenn, Boveri, and others that each parent transmits the same number of chromosomes to the zygote. Furthermore, the chromosomes in maternal and paternal nuclei appeared to be identical. These two observations could help explain the long-held belief that the hereditary contribution of each parent is roughly the same.

This was exciting and important research and soon many investigators were studying a large variety of plants and animals. With very few exceptions, what had been found for *Ascaris* was true for all other organisms. To be sure there were some minor variations, but an intensive study of these served only to increase the depth of our understanding of the entire process. A concept of universal application had been discovered.

PARADIGMS AND NORMAL SCIENCE

Thomas Kuhn (1970), in his *The Structure of Scientific Revolutions*, argues that science advances in two main ways which we might characterize as by fits and starts, or, to be more current, by punctuated equilibria. Kuhn points out that, from time to time, there is a revolution in the way scientists view their research problems and the sorts of observations and experiments that they undertake. Some bold, novel, and major new idea lets them see the existing data in a new perspective and suggests a new program of research. These major new ideas are, in Kuhn's terminology, *paradigms*—the "universally recognized scientific achievements that for a time provide model problems and solutions to a community of practitioners" (p. viii). The new paradigm is the central concern of the moment for a significant proportion of the scientists in a field. It determines the sorts of research they do and, in our times, whether or not they are likely to get grants. This work is the *normal science* that occupies most investigators most of the time. It consists of working out the consequences of the new paradigm.

We have discussed two major paradigms in cytology. The first was the Cell Theory, a new way of looking at the structure of organisms. That paradigm had a slow development but, in the first two-thirds of the 19th century, it occupied the attention of many cytologists. The normal science that was stimulated by the paradigm resulted in investigations of innumerable sorts of organisms and, almost always, their microscopic structure "made sense" in terms of Cell Theory.

These studies also extended the limits of what could be called "cell." The structure of tissues in human beings was investigated in great detail and soon this knowledge became of considerable importance in medicine as the basis of pathology. The structure of diseased cells and tissues became one of the most satisfactory criteria for identifying diseases. During the 19th century, diagnosis, not cure, was the crowning achievement of medicine. Physicians were far better in identifying diseases than in curing them.

Kuhn believes that in most instances one paradigm does not evolve into a new one. Instead, the field takes an entirely different approach with a new paradigm. Gradually the practitioners lose interest in the old paradigm and begin to work out the details of the new. Or most of the older scientists pass out of the picture with their old paradigm and the Young Turks do the normal science within the parameters of the new paradigm.

This happened in cytology. In the last third of the 19th century a new approach came into vogue. The new paradigm may be called the Theory of Chromosomal Continuity. It sought to trace the behavior of chromosomes in mitosis, meiosis, and fertilization. Many cytologists lost interest in establishing that yet another creature had a body composed of cells and, instead, sought to discover what that creature's

OUTLINE OF MEIOSIS AND

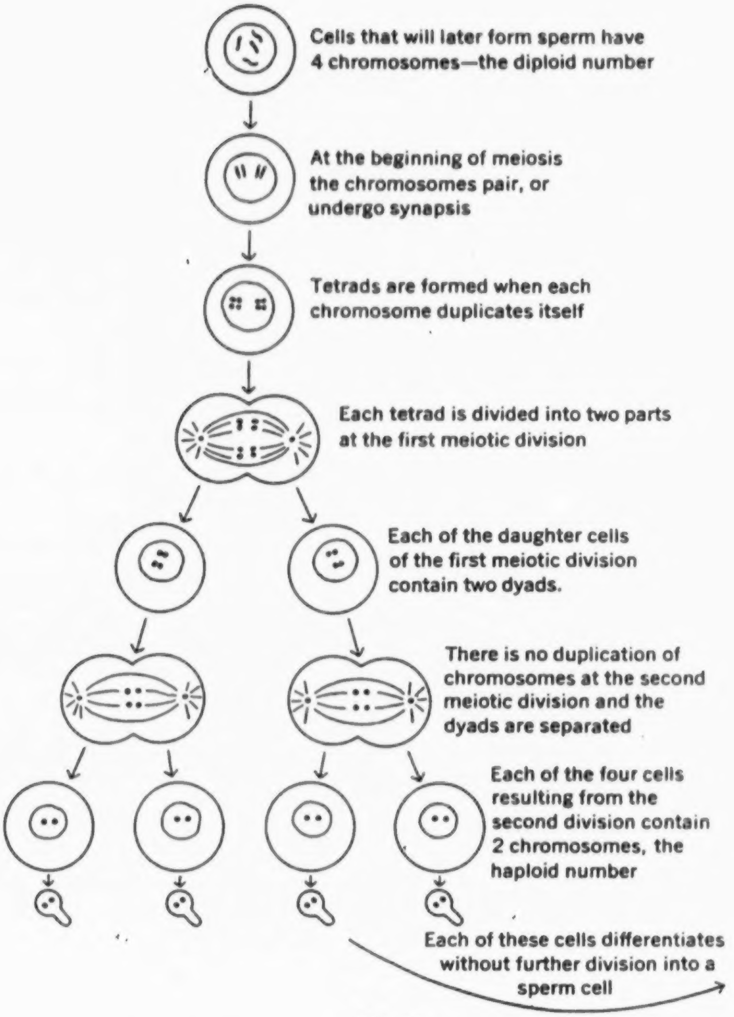

Cells that will later form sperm have 4 chromosomes—the diploid number
At the beginning of meiosis the chromosomes pair, or undergo synapsis
Tetrads are formed when each chromosome duplicates itself
Each tetrad is divided into two parts at the first meiotic division
Each of the daughter cells of the first meiotic division contain two dyads.
There is no duplication of chromosomes at the second meiotic division and the dyads are separated
Each of the four cells resulting from the second division contain 2 chromosomes, the haploid number
Each of these cells differentiates without further division into a sperm cell

FIG. 12.

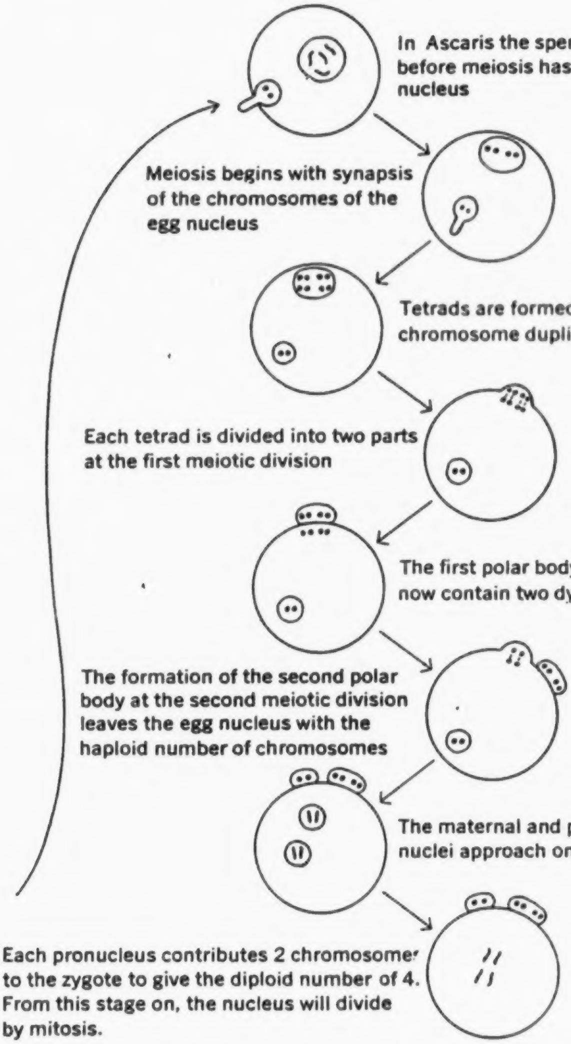
chromosomes did in the life cycle. Once again, the new paradigm provided a conceptual basis for important biological phenomena and guided the research, the normal science, that fleshed out the details.

Until fairly recent times, cytology was mainly a descriptive science. One's ability to manipulate cells to test hypotheses was severely limited. In many instances, however, it turned out that some species might exhibit the cellular condition sought by the investigator. Hence, nature had already arranged the experiment. It was mainly for this reason that cytologists studied a great variety of organisms to discover those that exhibited some variation in chromosomal behavior and, hence, might give tests of deductions when experimentation was not possible.

THE NUCLEUS AND INHERITANCE

The remarkable observations on the behavior of chromosomes in mitosis, meiosis, and fertilization made in the 1870s

FERTILIZATION IN ASCARIS



In Ascaris the sperm enters the egg before meiosis has begun in the egg nucleus

Meiosis begins with synapsis of the chromosomes of the egg nucleus

Tetrads are formed when each chromosome duplicates itself

Each tetrad is divided into two parts at the first meiotic division

The first polar body and the egg now contain two dyads each

The formation of the second polar body at the second meiotic division leaves the egg nucleus with the haploid number of chromosomes

The maternal and paternal nuclei approach one another

Each pronucleus contributes 2 chromosomes to the zygote to give the diploid number of 4. From this stage on, the nucleus will divide by mitosis.

FIG. 12. Continued.

and 1880s, mainly in Germany, provided a general picture for the transmission from generation to generation of the fundamental structures responsible for inheritance.

But I trust that your students will observe that those studies provided no *critical* evidence that chromosomes are, indeed, the physical basis of inheritance. One could do no more than suggest that the chromosomes *could* play that role. Nor in the 1880s were they any closer to being able to say how one might establish the role of a cellular structure in heredity.

Nevertheless, many scientists believed that the nucleus and/or the chromosomes were the prime candidates for this important biological function. As early as 1866 Ernst Haeckel (1834–1919) suggested that the nucleus is responsible for the transmission of what we call genetic information. This was really a long shot. It was still seven years before Schneider's description of mitosis in *Mesostoma*, and Haeckel had no data to support his hypothesis. Nevertheless Haeckel was one of the most prominent biologists of the day and any idea of his, no matter how slight the factual basis, would be noticed. Therefore, Haeckel's hypothesis of nuclear control of heredity would stimulate others to think along such lines.

Darwin's *Variation* was published two years later and, again, something was being said about inheritance by a very important scientist. The great difference between the hypotheses of Haeckel and Darwin indicated that the field was still wide open.

In 1884 still another important biologist, Carl Wilhelm von Nägeli (1817–1891), suggested a very different hypothesis. He postulated a material, the idioplasm, as the physical basis of inheritance. He proposed that it was an invisible chemical network extending throughout cells and from one cell to another. It could be imagined to be Darwin's gemmules joined to form a continuous web. He postulated that the idioplasm was somewhat unstable and could change during development but return to the original condition at the beginning of the next generation.

Nägeli expanded the hypothesis of the idioplasm into a huge theoretical structure without much basis in observation or experiment. In fact, the hypothesis was essentially impossible to test and, hence, of little use in furthering knowledge. It is mentioned here to show that, although some prominent biologists believed the nucleus to be the center of inheritance, other prominent biologists predicted other mechanisms. This is always the case at the frontiers of science. There will be a variety of competing explanatory hypotheses that will be tested, and, in time, one will remain the best explanatory hypothesis of the day. We mislead ourselves, and our students, if we treat the intellectual development of a field as a straight line to "truth." More often than not the model resembles not that straight line but Nägeli's idioplasm—going in all directions at the same time. But now back to the main line!

THE HYPOTHESIS OF CHROMOSOMAL CONTROL OF INHERITANCE

In 1884–1885 four German biologists independently concluded that the physical basis of inheritance must be the chromosomes. They were Oskar Hertwig, Edouard Strasburger, Rudolf Kölliker, and August Weismann. The first three were active investigators of cellular events centering around fertilization. Weismann, in part because of poor eyesight, was concerned mainly with theory—recall his prediction of the reduction divisions.

The basic problem for the student of the cell who sought the physical basis of inheritance was to find some cellular phenomenon that could account for what was known about inheritance. That is, how could one find in cells something that accorded with the results of breeding experiments? Expressed still another way, one had to discover some cytological phenomenon that would parallel genetic phenomena—an especially difficult task when there were no precise genetic rules.

The sorts of data and argument that suggested the hypothesis of chromosomal involvement in inheritance to the four biologists mentioned above were as follows.

First, it was usually observed that both parents seem to have an equal share in transmitting their characteristics to the offspring. (Darwin had emphasized this even while recognizing a few cases of sex-linked inheritance as well as other exceptions.)

A study by Joseph Gottlieb Kölreuter, the great plant hybridizer, was an excellent example. More than a century earlier, he had crossed two very different species of the tobacco genus, *Nicotiana paniculata* and *Nicotiana rustica*. It was important to use plants that differed considerably so that he could test the influence of each parent. So far as Kölreuter could tell the hybrids were the same whether the cross was *Nicotiana paniculata* pollen × *Nicotiana rustica* ovules or the reverse. Neither parent had a dominant role. (See Roberts [1929, ch. 2].)

What could be the basis of this equality found by Kölreuter and many others? In the case of animals there is a great difference in the quantity of material in ova and sperm. If the results of inheritance depended solely on the quantity of material transmitted by the female and by the male, and if their gametes were the sole physical link between the generations, then one would expect the female's influence on the offspring to be greater than the male's. Since this appears not to be so, the ovum as a whole and the sperm as a whole cannot be the physical basis of inheritance.

Is there, therefore, *any* cellular component of sperm and ovum that is equivalent? If so, it might be a candidate for a central role in inheritance. In the late 1880s a possible candidate was being suggested by the then most recent research. Hertwig and many others were finding that, shortly after fertilization, there were two nuclei—the female pronucleus and the male pronucleus. These appeared to be identical, apart from the centrioles and centrosome associated with the sperm pronucleus, so perhaps this equivalence in structure could be the basis of the equivalent importance of the two gametes in inheritance.

Second, there seemed to be both a stable and an unstable component to inheritance. In almost all ways offspring closely resembled their parents in general body structure. Thus, whatever was transmitted from parent to offspring via the gametes must have a high degree of stability. Yet offspring were rarely exactly like their parents and, moreover, the offspring might differ from one another.

There did seem to be a possible cellular basis for the stability—the chromosomes of the nucleus. During cell division the cytoplasm and its formed structures appear to be divided passively and by chance. That is, if a granule or globule happens to be at one end of the spindle, it ends up in the daughter cell including that material. The chromosomes, on the other hand, go through a complicated mitosis that results in each daughter cell apparently receiving an identical set of chromosomes. It seemed to Hertwig and the others that such precision in the distribution of the nuclear material during cell division could mean that the chromosomes were involved in transmitting the genetic information. There was no other likely candidate, except possibly the centrioles. But centrioles were so small and difficult to see that cytologists were not sure that they were present in all cells. They did not appear to be in ova just before fertilization and higher plants seemed to lack them.

Third, this same general argument could be applied to the chromosomal events during meiosis. The complex chromosomal changes during meiosis and fertilization could be looked upon as mechanisms for maintaining chromosomal constancy from generation to generation. Nothing like this was apparent for any other cell structure. Therefore, since inheritance is an intergeneration phenomenon and the chromosomes seem to be the only cell structures transmitted in such a precise manner as to maintain constancy, perhaps they are the key to inheritance.

Fourth, there was at least one type of experimental data. In some cases it was possible to cut protozoans into two parts—one part with the nucleus and the other without. Both parts may heal. The part with the nucleus was observed to regenerate any missing structures and to live as a normal, reproducing individual. On the other hand, the part without the nucleus did not regenerate to form a whole animal and it never reproduced. Its fate was death.

These observations were suggestive but they did not constitute complete proof that the nucleus, or its chromosomes, are the physical basis of inheritance. Furthermore, these observations could not explain many other aspects of inheritance—variation, for example. The fact that chromosomes appeared to be the only cell structures that remain constant from cell to cell, and from generation to generation, *could* mean that chromosomes are the structures of inheritance.

Weismann (1889) was willing to be far more definite than that. Recall the quotation previously given,

> . . . at least one certain result follows, viz.

> that there is an hereditary substance, a material bearer of hereditary tendencies, and that this substance is contained in the nucleus of the germ-cells, and in that part of it which forms the nuclear threads, which at certain periods appear in the form of loops or rods. (p. 355)

E. B. Wilson (1895, p. 4), in a most astonishing statement, foresaw the 1940s and 1950s.

> These facts justify the conclusion that the nuclei of the two germ-cells are in a morphological sense precisely equivalent, and they lend strong support to Hertwig's identification of the nucleus as the bearer of hereditary qualities. The precise equivalence of the chromosomes contributed by the two sexes is a physical correlative of the fact that the two sexes play, on the whole, equal parts in hereditary transmission, and it seems to show that the chromosomal substance, the *chromatin,* is to be regarded as the physical basis of inheritance. Now, chromatin is known to be closely similar to, if not identical with, a substance known as *nuclein* ($C_{29}H_{49}N_9P_3O_{22}$, according to Miescher), which analysis shows to be a tolerably definite chemical composed of nucleic acid (a complex organic acid rich in phosphorus) and albumin. And thus we reach the remarkable conclusion that inheritance may, perhaps, be effected by the physical transmission of a particular chemical compound from parent to offspring.

Prophetic yes, but at the time a hypothesis that could not be tested. In reality, attempts to use the data of cytology alone to understand inheritance appeared to have come to a dead end. How was one to establish a causal link between the data of inheritance derived from breeding experiments and the behavior of chromosomes? For that matter, the study of inheritance by breeding experiments had come to a dead end as well. Both cytology and, what we would now call genetics, were in the Kuhnian stage of normal science awaiting the arrival of a new paradigm. That was to occur, in a most dramatic fashion, in the year 1900.

But before we move into the 20th century we can conclude with this summary by E. B. Wilson of what had been accomplished in the flowering of cytology that occurred in the last quarter of the 19th century.

> The work of cytology in its period of foundation laid a broad and substantial basis for our more general conceptions of heredity and its physical substratum. It demonstrated the basic fact that heredity is a consequence of the genetic continuity of cells by division, and that the germ-cells are the vehicle of transmission from one generation to another. It accumulated strong evidence that the cell-nucleus plays an important role in heredity. It made known the significant fact that in all the ordinary forms of cell-division the nucleus does not divide *en masse* but first resolves itself into a definite number of chromosomes; that these bodies, originally formed as long threads, split lengthwise so as to effect a meristic division of the entire nuclear substance. It proved that fertilization of the egg everywhere involves the union or close association of two nuclei, one of maternal and one of paternal origin. It established the fact, sometimes designated as "Van Beneden's law" in honour of its discoverer, that these primary germ-nuclei give rise to similar groups of chromosomes, each containing half the number found in the body-cells. It demonstrated that when new germ-cells are formed each again receives only half the number characteristic of the body-cells. It steadily accumulated evidence, especially through the admirable studies of Boveri, that the chromosomes of successive generations of cells, though commonly lost to view in the resting nucleus, do not really lose their individuality, or that in some less obvious way they conform to the principle of genetic continuity. From these facts followed the far-reaching conclusion that the nuclei of the body-cells are diploid or duplex structures, descended equally from the original maternal and paternal chromosome-groups of the fertilized egg. Continually receiving confirmation by

> the labours of later years [*i.e.*, normal science], this result gradually took a central place in cytology; and about it all more specific discoveries relating to the chromosomes naturally group themselves . . . . Such, in bird's-eye view, were the most essential conclusions down to the close of the nineteenth century. A new era of discovery now opened [the new paradigm]. As soon as the Mendelian phenomena were made known it became evident that in broad outline they form a counterpart to those which cytology had already made known in respect to the chromosomes. (pp. 334–335)

The quote is from Wilson's famous Croonian Lecture to the Royal Society of London. It was given in 1914 by which time the hypotheses concerning the relations of chromosomes had been tested and proven true beyond all reasonable doubt.

REFERENCES TO 19TH CENTURY CYTOLOGY

The most useful single reference is J. R. Baker's (*1948–1955) series *The Cell Theory.* For a fine, though shorter, paper see Coleman (*1965). The *1900 edition of E. B. Wilson's *The Cell in Development and Inheritance* summarizes the field just before the Mendelian results became generally known. And for the grand sweep see Mayr (*1982).

See also Ackernecht (1953), Allen (1976), Baltzer (1964, 1967), Blumenbach (1742), Bracegirdle (1977, 1978), Carlson (1967*a*), Carpenter (1891), Chubb (1910–1911), Churchill (1968), Coleman (1971), Conklin (1939), Dobell (1960), Emblen (1970), 'Espinasse (1962), Gabriel and Fogel (1955), Gerlach (1858), Gerould (1922), Glass (1947), Grew (1682), Gunther (1930–1938), Haeckel (1866), Hall (1969), Hertwig (1895), Holmes (1963), Hooke (1665), Hughes (1959), Huxley (1853, 1868), Karling (1939), Kisch (1954), Kölliker (1853–1854), Mark (1881), Mazzeo (1967), Moore (1972*a*, 1972*b*), Nicolson (1956), Pickstone (1973), Power (1664), Rich (1926), Robinson (1979), Roget (1836), von Sachs (1890), Schleiden (1838, 1842), Schwann (1839, 1847), Scott (1891), Shadwell (1676), Singer (1915), Sirks (1952), Strasburger (1880), A. Thomson (1836–1839), Todd (1836–1839), Virchow (1863), Voeller (1968), Weismann (1889, 1891–1892, 1893), Wilkie (1960), E. B. Wilson (1895, 1899, 1900, 1914), J. W. Wilson (1944, 1947*a*, 1947*b*), and Woodruff (1939).

References to microscopes and cytological techniques were given earlier.

CYTOLOGY AND GENETICS: 1900–1910

Born again Mendelism

1900 is the year of the onset of modern genetics. It was then that a modest, unappreciated, and nearly-to-be-forgotten paper by a long-dead Augustinian monk became known to the scientific community at large. The field of animal and plant breeding had been in a long and unexciting Kuhnian period of "normal science" but in 1900 there was to be a notable paradigm shift and genetics was on its way to become a rigorous science with vast explanatory and predictive abilities. The new paradigm was to start with the discovery of a long-overlooked paper, *Versuche über Pflanzen-Hybriden,* based on lectures that Gregor Mendel delivered to the Natural History Society of Brünn (now Brno in Czechoslovakia) on 8 February and 8 March 1865 and published in 1866 (with a publication date of 1865).

The story is familiar to teachers of biology and a convenient source of the basic documents is provided by Stern and Sherwood (1966). Two scientists, Hugo de Vries (1900) and Carl Correns (1900), are credited as being the first to understand the importance of what Mendel had accomplished. A third scientist, Erik von Tschermak, is usually included as a co-first-appreciator but Stern and Sherwood (1966, pp. x–xi) give reasons why this is not merited.

De Vries had crossed numerous "species" and varieties of plants during the 1890s. In those days the term "species" was sometimes applied to different domesticated plants that we would now consider as belonging to the same species but differing by one or a few alleles with large effects. De Vries adopted the point of view that these different "species" should be considered "as a composite of independent factors," or units, and that,

> The units of species-specific traits are to be seen in this connection as sharply separate entities and should be studied as such. They should be treated as independent of each other everywhere, as long as there is no basis for doing otherwise. In every crossing experiment only a single character or a definite number of them is to be taken into consideration. (Stern and Sherwood, p. 108)

De Vries spoke of antagonistic characters but noted that only one was expressed in the hybrid (*i.e.*, in the F_1). Nevertheless when the pollen and ovules were formed "the two antagonistic characteristics separate, following for the most part simple laws of probability" (Stern and Sherwood, p. 110).

De Vries stated that his essential conclusions had been reached long before by Mendel, whose work had been forgotten and its significance not understood.

The story of how de Vries came to know of Mendel's paper is of considerable interest (Stomps, 1954). He did not uncover it through a "literature search" but by one of those extraordinary accidents that seem to be of such importance in scientific discovery. A fellow Dutch scientist, Professor Beyerinck of Delft, knew that de Vries had been hybridizing plants and wrote wondering if he would be interested in an old reprint dealing with the same subject. It was Mendel's paper. The letter and reprint reached de Vries in 1900, just as he was preparing to publish his own experiments. He was able to do so knowing that he was confirming Mendel's earlier, and more extensive, experiments.

The story about Correns is equally interesting (Stern and Sherwood, 1966). He also had been performing genetic experiments with plants and was trying to develop a hypothesis to account for the data. In the autumn of 1899 the solution came to him in a "blind flash," which, more often than not, seems to be the origin of the truly important breakthroughs in science. A short time later he found a reference to Mendel's paper and looked it up. He published his own data and showed how it confirmed what Mendel had found.

Perhaps it is time for us, also, to see what Mendel had done.

Mendel 1865

Gregor Mendel's famous paper is not a scientific paper in the usual sense, but instead lectures that he presented to the Natural History Society of Brünn in 1865. The complete data were never published but the portion that he did include, coupled with his extraordinary analysis of the data, puts his contribution in the same class as *On the Origin of Species.*

Mendel was fully aware that experiments in plant breeding, usually called hybridization, had been conducted for years by many famous scientists. No general rules had emerged, as we have already seen from Darwin's lack of success in *Variation . . .*, published only two years after Mendel's paper.

Mendel had started his experiments trying to understand inheritance shortly after the publication of Darwin's *Origin* and one of the reasons for so doing was the need for "reaching the solution to a question whose significance for the evolutionary history of organic forms must not be underestimated." Thus, Mendel's work started out as normal science within the paradigm of the Theory of Evolution. Only later was it to become the beginning of a new paradigm—Mendelian Genetics. This is an interesting point for students: how a discovery in one field of science may be of great importance in another.

The experimental material

Plant hybridizers of the mid-19th century had a wealth of readily available material. Numerous varieties of the same species of both food and ornamental plants had been selected. Many of the varieties were very different from one another—so different that they might be given their own scientific names. Once varieties had been developed, continued selection was practiced so they would "breed true."

Mendel decided to work with garden peas and started with 34 varieties. He grew them for two seasons to make sure that they bred true. Finally he reduced the number to 22 varieties.

Peas had important advantages. Not only were many varieties available, as already noted, but they were easy to grow and had short generation times. The offspring obtained by crossing the varieties were fertile. The structure of the flower was also important. The stamens and pistils are enclosed by the sepals and petals and, if the flowers were covered to prevent insects from reaching them, they self-fertilize, that is, pollen falls on the stigma of the same flower.

Nevertheless, experimental crosses could be made. This was done by removing the anthers before they matured and, later, placing pollen from another plant on the stigma. Thus, Mendel could cross any of his varieties or, if he left the flowers alone, the next generation would be a consequence of self-fertilization.

Mathematics for Mendel

Those who have taught Mendelian genetics will know that many students find the mathematics difficult. It may become easier for them when, in 1903, we will put the hereditary units on the chromosomes, but it is worth the effort to help students understand such critical aspects of the Mendelian model as how the 3:1 ratio for one pair of contrasting characters can be expanded to the 9:3:3:1 ratio for two pairs of contrasting characters.

It has been my experience that one of the most difficult principles that students have to learn is that ¼ of ¼ is neither ½ nor ⅛ but $\frac{1}{16}$. In addition, students must come to believe that a 3:1 ratio is the same as saying that ¾ of the sample is of one sort and ¼ of the sample is of another sort or that 75 percent is one and 25 percent is another. A determined but sympathetic teacher can usually bring about $\frac{15}{16}$ of the class to this level of achievement.

In the discussion of Mendel's experiment that follows a great deal of attention will be paid to presenting the material in a manner that may help students to understand, and truly appreciate, the elegance of what Mendel accomplished. It was first-rate science and it is a great pity that many can learn Mendel's method but not the workings of his mind.

Mendel's data

In genetic crosses we attempt to discover the hereditary basis of differences; at the same time we suspect that the information obtained will also help us to understand why individuals of the same species resemble each other so closely. One does not cross genetically identical individuals in the hope of discovering laws of inheritance. Thus the varieties of Mendel's peas differed from one another. The difference was in relation to the characteristics of other varieties. Thus some of his varieties had round seeds and in others the seeds were wrinkled ("angular" would be a better translation of his term); some of his varieties had yellow seeds and in others they were green. In all he used 7 pairs of contrasting characters as follows:

Character affected	Varieties
Seed shape	*round* or *wrinkled*
Seed color	*yellow* or *green*
Seed coat	*colored* or *white*
Pod shape	*inflated* or *wrinkled*
Pod color	*green* or *yellow*
Flower position	*axial* or *terminal*
Stem length	*long* or *short*

Varieties with the contrasting characters were crossed by removing the immature anthers from the flowers of one variety and placing pollen from the other variety on the stigma. The F_1, to use a term introduced subsequently, gave a uniform result: all of the F_1 exhibited the characteristic of only one parent. Mendel spoke of the characteristic that appeared in the F_1 as being *dominant*, in contrast the characteristic that did not appear—the *recessive*.

These results, so familiar to us today, were rather unexpected in the 1860s. Although there were similar instances, the general rule was that the F_1 individuals tended to be intermediate. And in most cases they are, for the simple reason that, if varieties differ in many ways, the F_1 will usually be more or less intermediate. But Mendel concentrated on the inheritance of details, not of the totality. In a sense he forgot the whole plant and asked only if the peas had *round* or *wrinkled* seeds, etc.

The F_1 plants were protected from being cross-pollinated by insects and allowed to self. Again the results were uniform. For each of the original seven crosses of plants with contrasting characters, the F_2 offspring resembled one or the other parent of the P generation. They were never intermediate.

Whereas most plant breeders would have reported only that both varieties appeared in the F_2, Mendel did a simple and revolutionary thing. He counted the numbers of individuals with each characteristic. The results for the seven types of crosses were the same: a ratio of 3 plants with the dominant characteristic to 1 with the recessive. Or we might say ¾ (75 percent) showed the dominant characteristic and ¼ (25 percent) the recessive characteristic.

These ratios and percentages were derived from the data. In the case of a cross of pure breeding plants with *round* seeds with pure breeding *wrinkled* seeds, the F_2 produced 5,474 *round* and 1,850 *wrinkled*, a ratio of 2.96 to 1. The *yellow* × *green* cross gave an F_2 of 6,022 *yellow* and 2,001 *green*, a ratio of 3.01 to 1. As we shall see, Mendel had reason to suspect that the theoretical answer would be 3 to 1 and not 3.01 to 1. These are monohybrid crosses.

When Mendel followed the inheritance of two pairs of contrasting characteristics, the dihybrid cross, uniform results were again obtained. The F_1 exhibited the two dominant characteristics only and the F_2 exhibited all four characteristics in the now familiar 9:3:3:1 ratio. That is, $\frac{9}{16}$ of the F_2 showed both dominant characteristics, $\frac{3}{16}$ showed one dominant and one recessive, $\frac{3}{16}$ showed the other dominant and other recessive, and $\frac{1}{16}$ had both recessive characteristics.

Thus, if the original P generation cross had been *round-yellow* × *wrinkled-green*, all of the F_1 would be *round-yellow*. In the F_2 he obtained 315 *round-yellow*, 108 *round-green*, 101 *wrinkled-yellow*, and 32 *wrinkled-green*. For this total of 556, the ratios of different kinds are 9.8:3.4:3.2:1. Those ratios represent the real data but Mendel proposed a hypothesis that suggested in a theoretically ideal experiment the ratios would be 9:3:3:1.

Now our problem is to analyze how the 3:1 ratio is related to the 9:3:3:1 ratio.

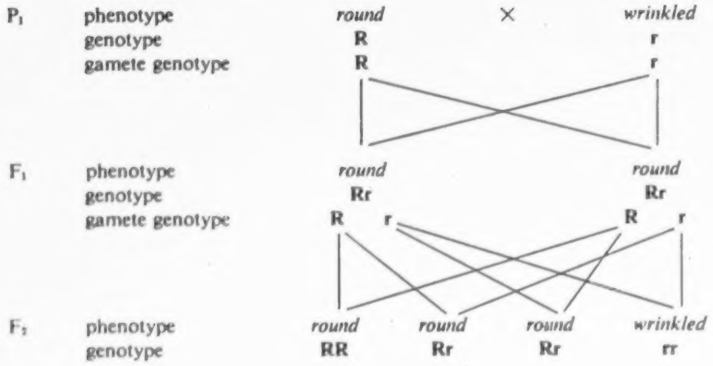
In a cross of *yellow* × *green*, the F_2 will be ¾ *yellow* and ¼ *green*. Similarly, in a cross of *round* and *wrinkled*, the F_2 will be ¾ *round* and ¼ *wrinkled*. Many students asked to predict the F_2 ratios of a dihybrid cross, *round-yellow* × *wrinkled-green*, may find the problem insoluble at first.

The following analysis will usually work. When two, or even more, pairs of contrasting characteristics are involved, one must recognize that the 3:1 ratio still holds for the individual characteristics. In the cross already discussed that gave a 9:3:3:1 ratio for two pairs of characteristics, the ratio is still 3:1 for the single characteristics. Consider the cross that gives $\frac{9}{16}$ *round-yellow*, $\frac{3}{16}$ *round-green*, $\frac{3}{16}$ *wrinkled-yellow*, and $\frac{1}{16}$ *wrinkled-green*. Considering *round* and *wrinkled* separately, we find $\frac{9}{16} + \frac{3}{16} = \frac{12}{16}$ that are *round* and $\frac{3}{16} + \frac{1}{16} = \frac{4}{16}$ that are *wrinkled*. Since $\frac{12}{16} = ¾$ and $\frac{4}{16} = ¼$, we observe a 3:1 ratio for the single pair. The same holds true for the *yellow* and *green* pair.

If we then ask what are the fractions in the F_2 that will result from a dihybrid cross, the answer comes from a simple multiplication of the fractions for the separate characters. Thus, of the ¾ that will be *round*, ¾ of them will also be *yellow* and ¼ will also be *green*. Therefore ¾ × ¾, or $\frac{9}{16}$, will be both *round* and *yellow* and ¾ × ¼, or $\frac{3}{16}$, will be both *round* and *green*. Of the ¼ of the F_2 that are *wrinkled*, ¾ will also be *yellow* and ¼ will also be *green*. Therefore ¼ × ¾, or $\frac{3}{16}$, will be *wrinkled-yellow* and ¼ × ¼, or $\frac{1}{16}$, will be *wrinkled-green*. That is the derivation of the 9:3:3:1 ratio.

Students may be interested in using this method to find the ratios for crosses involving three or four pairs of contrasting characters.

These striking regularities were observed by Mendel in all of the crosses. Therefore, he thought there must be some underlying principle.



		POLLEN 50% R	 50% r
OVULES	50% R	25% RR	25% Rr
	50% r	25% Rr	25% rr

FIG. 13. Model for a Mendelian monohybrid cross. The genotypes of the P generation individuals are as Mendel would have shown them. The genetic checkerboard at the bottom shows the origin of the F_2 (genotypes as we would show them today) from the F_1 pollen and ovules.

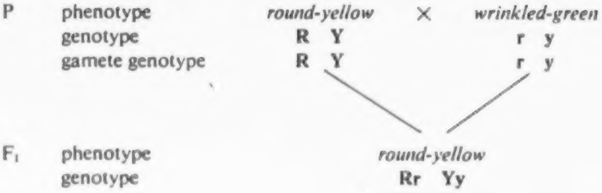
Model for the monohybrid cross

There was. Figure 13 is a model for the explanatory hypothesis that Mendel proposed to account for monohybrid crosses. Both the scheme and the terminology were to become standard half a century later in the early 1900s.

The first thing that an alert reader is likely to note is the "error" in the genotypes of the P generation. They are shown as monoploid instead of diploid and this brings up a very important point in our survey of genetic concepts. Mendel used the symbols for genotype to indicate *kinds* of hereditary factors, not *number* per gamete. The *round* parents' gametes could have contained innumerable **R** factors, not just 1 as we now believe. Thus the pure-breeding *round* plants produced only *round* offspring when selfed. The upper case and lower case letters indicate that the allele is dominant or recessive.

There can be only one type of offspring **Rr**, since there is only one type of pollen and one type of ovule. When these F_1 plants mature, each flower will produce ovules and pollen. Now comes one of the most important features of Mendel's model: he assumed that a gamete could have hereditary factors of only one kind, that is, in this cross a gamete would have **R** or **r** but not both (Fig. 13). This was to prove to be a very difficult problem for geneticists in the early 1900s. Their minds had been influenced by the concept of innumerable gemmules. How could a gamete be "pure" so to speak—have gemmules of only type **R** or type **r**?

Thus the F_1 individuals were assumed to produce gametes that had either **R** or **r**,



POLLEN

OVULES	RY	Ry	rY	ry
RY	**RR YY** *round-yellow*	**RR Yy** *round-yellow*	**Rr YY** *round-yellow*	**Rr Yy** *round-yellow*
Ry	**RR Yy** *round-yellow*	**RR yy** *round-green*	**Rr Yy** *round-yellow*	**Rr yy** *round-green*
rY	**Rr YY** *round-yellow*	**Rr Yy** *round-yellow*	**rr YY** *wrinkled-yellow*	**rr Yy** *wrinkled-yellow*
ry	**Rr Yy** *round-yellow*	**Rr yy** *round-green*	**rr Yy** *wrinkled-yellow*	**rr yy** *wrinkled-green*

FIG. 14. Model for a Mendelian dihybrid cross. The genotypes of the P generation are as Mendel would have shown them. The genetic checkerboard shows the origin of the F_2 (genotypes as we would show them today) from the F_1 pollen and ovules.

but never both. Mendel next assumed that ovules and pollen grains would combine at random and that the kinds of offspring would be in frequencies determined by the frequencies of the different kinds of gametes.

It must be emphasized to students that the apparent simplicity of the scheme is shown in Figure 13, of the origin of the F_2 from the gametes of the F_1, works only because the genotypic classes of both ovules and pollen are in equal frequency. That is, each produces 50 percent **R** pollen (or ovules) and 50 percent **r** pollen (or ovules). The lines are so drawn that all possible combinations occur and they do so in equal frequency. The **R** gamete on the left, for example (let's pretend that it is a pollen grain), has an equal chance of combining with either an **R** or an **r** ovule. The same is true for the **r** pollen.

The genetic checkerboard at the bottom of Figure 13 is another conventional way of helping students to understand Mendel's hypothesis for the 3:1 ratio in the F_2 of a monohybrid cross.

The model applies to *all* of the crosses involving a single pair of contrasting characters. The model will account for the data only if the following conditions hold:

1. In each pair of contrasting hereditary units, one member of the pair is dominant and the other recessive. Dominance and recessiveness are operational definitions—determined by the phenotype of an individual that has both types of hereditary units.

2. The dominant and recessive hereditary characteristics do not modify one another in any permanent way when they exist together. Thus, in the F_1 the **r** factors from the *wrinkled* parent in the cross of Figure 13 are combined with **R** factors from the *round* parent. There is no expression

of the **r** factors in the F_1 but in the F_2 one quarter of the individuals are *wrinkled*—and just as wrinkled as the *wrinkled* grandparent.

3. By some mechanism unknown to Mendel the two sorts of factors in the F_1 segregate in such a manner that each gamete contains only one sort. Thus in the example, the gametes will contain **R** or **r**.

4. By still another unknown mechanism the **R** containing gametes and the **r** containing gametes are produced in equal numbers.

5. Combinations between the pollen and ovules are entirely at random and the frequencies of the offspring will depend on the frequencies of the different classes of gametes.

Testing the hypothesis

It should be emphasized that the congruence of data and model is not fortuitous. Although items 1 and 2 above could be accepted as true, items 3–5 were entirely hypothetical—they were invented to explain the data. This is perfectly acceptable scientific procedure. The model is to be regarded as a tentative explanation, a hypothesis, that will stand or fall on the basis of tests of deductions made from it.

One critical test was easy to make. The F_2 individuals in the Figure 13 cross consist of 3 plants showing the dominant *round* characteristic to every 1 showing the recessive *wrinkled* characteristic. However, if the hypothesis is true, the *round* seeds must be of two sorts and in a predictable ratio. Thus, for every seed that has the **R** genotype (remember we are still using the Mendelian scheme, so do not say **RR**), there will be two that are **Rr**.

There is no way of distinguishing visually between an **R** and an **Rr** seed, but if the seeds are planted and the flowers allowed to self-fertilize, the offspring will give the answer. Thus the **R** genotype should breed true and the **Rr** genotype should give a 3:1 ratio of *round* to *wrinkled*. Mendel planted the seeds and found this to be true.

Model for the dihybrid cross

Figure 14 shows the model for the dihybrid cross discussed before. A pure breeding *round-yellow* plant is crossed with a pure breeding *wrinkled-green*. The F_1 individuals are uniform—showing the dominant phenotype of both pairs of contrasting characters.

In the formation of gametes by the F_1, Mendel assumed, as for the monohybrid cross, that each gamete would receive only one type of the two contrasting units—either **R** or **r**. The same was assumed to be true for **Y** and **y**. At this point, still another assumption had to be made: there would be an independent assortment of both pairs. Thus each gamete would have either **R** or **r** and, in addition, either **Y** or **y**. There would then be four classes of both pollen and ovules: **RY**, **Ry**, **rY**, and **ry**. The model also demanded that these classes be in equal frequency—25 percent for each.

If students have trouble understanding the origin of the four classes of gametes, a simple game with two different coins—a penny and nickel perhaps—may help. Let each coin represent a gene and the "head" represent the dominant allele and the "tail" the recessive allele. The coins are then tossed and the results recorded. If enough throws are made, one expects ¼ to be heads for both coins (*i.e.*, the **RY** category above); ¼ will be tails for both coins (*i.e.*, the **ry** category above); ¼ will be heads for the penny and tails for the nickel (=**Ry**); and ¼ will be tails for the penny and heads for the nickel (=**rY**).

When there are four classes of gametes, it is not practical to use the lines, as in Figure 13, so in the lower part of Figure 14 there is a genetic checkerboard showing all possible combinations of pollen and ovules that produce the F_2 (for simplicity all genotypes are now shown as diploid). There are 16 boxes in the checkerboard and, if the phenotypes are combined, we find that 9 of the 16 are *round-yellow*, 3 are *round-green*, 3 are *wrinkled-yellow* and 1 of the 16 is *wrinkled-green*. That accounts for the 9:3:3:1 ratio.

Notice that only *round-yellow* and *wrinkled-green* phenotypes were present in the P and F_1 generations. The model demands, however, that two *new* types of seeds appear: *round-green* and *wrinkled-yellow*.

Here are the data that Mendel reported for the F_2.

	Actual	Expected
round-yellow	315	313
round-green	108	104
wrinkled-yellow	101	104
wrinkled-green	32	35

The "actual" numbers are the counts of the seeds. The "expected" are the numbers in a perfect 9:3:3:1 ratio. The agreement of actual and expected is remarkably good, as Weldon and Fisher were to note years later.

Further tests of the hypothesis

The model for the dihybrid cross allowed even more elegant testing of the hypothesis. The hypothesis predicted that, except for the 32 *wrinkled-green* seeds, all other classes while looking the same consisted of genetically different individuals. This could be tested by planting the F_2 seeds, allowing the plants to self-fertilize, and then counting the F_3 seeds.

Consider first the 32 *wrinkled-green* seeds. The model predicts that these will breed true if selfed. The seeds were planted and 30 grew. All proved to be *wrinkled-green.*

The 101 *wrinkled-yellow* seeds were identical so far as the eye could tell. We can see from the model in Figure 14 that 3/16 are in this category but two genotypes are represented: 1 of the 3 is **rrYY** and the other 2 are **rrYy** (Mendel would have listed the **rrYY** as **rY** but for simplicity I am using the genotypes as shown in the figure). Thus 1 out of every 3 of the seeds, the **rrYY** class, would be expected to breed true and produce only *wrinkled-yellow.* Two of the 3, the **rrYy** class, would be expected to produce offspring in a ratio of 3 *wrinkled-yellow* to 1 *wrinkled-green.* The 101 seeds were planted and 96 grew. Of these, 28 (32 expected) produced all *wrinkled-yellow* and 68 (64 expected) produced *wrinkled-yellow* and *wrinkled-green* in a ratio of 3:1. Thus the deduction from the hypothesis was found to be true.

The same analysis was done for *round-green.* The 3/16 belonging to this class were predicted to consist of 1 **RRyy** and 2 **Rryy**. The 1/3 that were **RRyy** should breed true. The 2/3 that were **Rryy** should produce seeds in a ratio of 3 *round-green* and 1 *wrinkled-green.* The 108 seeds were planted and 102 grew. One would have expected 34 to breed true and 68 to give the 3:1 ratio. The actual numbers were 35 and 67.

The most complex test of the hypothesis was based on the 9/16 of the F_2 that were *round-yellow.* A check of the checkerboard shows that 1 of the 9 is **RRYY**, 2 are **RRYy**, 2 are **RrYY**, and 4 are **RrYy**. Thus, only 1 of the 9, the **RRYY** class, should breed true. The **RRYy** should give offspring in a ratio of 3 *round-yellow* to 1 *round-green.* The **RrYY** should produce 3 *round-yellow* to 1 *wrinkled-yellow.* And finally the **RrYy**, which are the same as the F_1 in Figure 14, should give a 9:3:3:1 ratio. The 315 seeds were planted and 301 produced a crop. The model predicts that the actual numbers in each class (in the order just listed) should be 33, 67, 67, and 134. For example, 1/9, or 33 seeds, should have bred true since the model predicts that number of seeds should have been **RRYY**. Mendel found the actual numbers to be 38, 65, 60, and 138.

The fact that the F_2 gave an F_3 that did not differ significantly from the hypothesis in these rather demanding tests of the deductions is strong support for the validity of the hypothesis. In every case the actual numbers are very close to the expected numbers. The expected numbers are based on the probability of the gametes behaving according to strict rules. The expected and actual numbers were never identical. We should not expect them to be so any more than we should always expect to get 5 heads and 5 tails for every 10 tosses of a coin.

Conclusions

Mendel's experiments on crossing varieties of peas and his remarkable analysis of the data permit the following eight major conclusions. It is important for students to realize that, in 1865, the conclusions were for peas and peas only. To be sure, Mendel had made some preliminary crosses with beans but the results were confusing.

First, the most important conclusion is that inheritance appears to follow definite and rather simple rules. Mendel proposed a model that would account for the data of all his crosses. Furthermore, the model had great predictive value—a goal of all hypotheses and theories of science.

Second, when plants of two different types are crossed, there is no blending of the individual characteristics. Of the seven pairs of contrasting characteristics, one type was dominant and the other recessive. That is, in a hybrid formed by crossing a pure breeding plant having the dominant characteristic with a pure breeding plant having the recessive characteristic, the offspring are uniform in appearance and identical with the dominant parent.

Third, since the hybrid described above is identical in appearance with the pure breeding dominant parent, we can conclude that there is not an exact relation between genotype and phenotype. Thus, the *round* phenotype can be based on either an **RR** (Mendel would have said **R**) or **Rr** genotype.

Fourth, the hereditary factors responsible for the dominant and recessive condition are not modified by their occurrence together in a hybrid. If two such hybrids are crossed, both dominant- and recessive-appearing offspring will be produced, and these offspring show no evidence that the hereditary factors responsible for their appearance have been modified by their association in the parents. An F_2 individual with the recessive phenotype will be identical to the phenotype of the original P generation recessive.

Fifth, when hybrids such as **Rr** are crossed, the two types of hereditary units—**R** and **r**—segregate from one another, and at fertilization recombine at random. The offspring will be in a phenotypic ratio of 3:1 and genotypically there will be, using the modern convention for genotypes, 1 **RR**, 2 **Rr**, and 1 **r**. Segregation is often called "Mendel's First Law."

Sixth, this ratio can occur only if each gamete receives only one type of hereditary factor—in the example either **R** or **r**.

Seventh, when crosses involve two pairs of contrasting hereditary units, such as **RrYy** crossed with **RrYy**, each pair behaves independently. That is, the different types of hereditary units assort independently of one another, so the gametes can be only **RY**, **Ry**, **rY**, or **rr**. Thus all possible combinations will be obtained, with the strict rule that each gamete can have only one kind of each of the pairs of hereditary units. The different classes of gametes will be in equal frequency. This phenomenon of independent assortment is known as Mendel's Second Law.

Eighth, the Mendelian hypothesis, and its formulation in a model, was so specific that deductions could be made and these could be tested by observation and experiment. No other field of experimental biology had reached an equivalent stage of development in 1865.

But, as we have seen, at that time no biologist seemed to realize that such was the case. To be sure, Mendel's work would not have been important if it had applied only to garden peas—any more than Hooke's discovery of cells would have been important had cells been observed only in cork. The field of plant breeding was full of data from which no general conclusions could be drawn. Mendel wrote to a foremost scholar in the field, Nägeli, and explained his results. Nägeli must have regarded the data for peas as just one more example of the tremendous variation in the results obtained in hybridization experiments.

Nägeli suggested that Mendel try another plant—*Hieracium*, the hawkweed. Mendel did and failed to find consistent rules for inheritance. It turned out that Mendel had not been doing the experiments he assumed he was doing. It was exceedingly difficult to make experimental hybrids in *Hieracium* with its tiny flowers. Nevertheless Mendel thought he had done so in many instances and was surprised at the lack of uniformity in the results. The problem was with *Hieracium*, not Mendel. Long after Mendel's death it was discovered that a type of parthenogenetic development, apomixis, occurs in *Hieracium*. No uniform ratios are to be expected if some of the offspring are the result of fertilization and others of apomixis.

So even Mendel came to believe that his results had a restricted application and, in any event, his model was ignored during the last third of the 19th century. During those decades the leading students of heredity had abandoned the paradigm of experimental breeding and concerned themselves mainly with the behavior of chromosomes in meiosis, mitosis, and fertilization. They believed that they were laying a physical basis for inheritance and further research was to prove them correct.

Mendel in retrospect

Much is usually made of the fact that Mendel's seminal work had been published in an obscure journal of an obscure society, so that it was either forgotten or unknown for 35 years—a 35 years that saw the flowering of cytology and intense interest in heredity. A more accurate statement would be, I suspect, that the paper was unappreciated rather than unknown. It was known to Focke (1881) who discussed it briefly in his standard treatment of plant hybridization and it was mentioned later by Bailey (1895). As already noted, Mendel had corresponded with one of the most prominent students of heredity at the time, Karl Wilhelm von Nägeli. Nägeli seemed not to be impressed with the data of Mendel's crosses of varieties of garden peas.

Bateson's explanation, taken from his introduction to Mendel's paper (Mendel, 1902, p. 2), was as follows:

> It may seem surprising that a work of such importance should so long have failed to find recognition and to become current in the world of science. It is true that the journal in which it appeared is scarce, but this circumstance has seldom long delayed general recognition. The cause is unquestionably to be found in the neglect of the experimental study of the problem of Species which supervened on the general acceptance of the Darwinian doctrines. The problem of Species, as Gartner, Kölreuter, Naudin, Mendel, and the other hybridists of the first half of the nineteenth century conceived it, attracted thenceforth no workers. The question, it was imagined, had been answered and the debate ended. No one felt any interest in the matter. [A paradigm shift!] A host of other lines of work were suddenly opened up, and in 1865 the more vigorous investigators naturally found those new methods of research more attractive than the tedious observations of the hybridisers, whose inquiries were supposed, moreover, to have led to no definite result. But if we are to make progress with the study of Heredity, and to proceed further with the problem "What is a Species?" as distinct from the other problem "How do Species survive?" we must go back and take up the thread of inquiry exactly where Mendel dropped it.

And, as we shall see, that is exactly what Bateson did.

Mendel's work on peas is not an isolated example of an important discovery being made but not understood by the scientific community at the time it was announced. New paradigms are not readily identified and adopted. Most scientists at any one time will be busy doing their normal science within the existing paradigm. The difficulty in changing what one does with hand and mind promotes resistance to new ideas and to the undertaking of new research programs.

This was not a problem for de Vries and Correns in 1900. The reason that they understood the importance of Mendel's conclusions is that they had done similar work and had developed a similar explanatory hypothesis before they read of Mendel's paper. They were working on the new paradigm before they knew of their paradigmatic progenitor.

The same point can be made for Bateson. He had been studying variation and hybridization for years, and although he had not observed the regularities of the Mendelian model, he knew the sorts of experiments that needed to be done. Consider the following.

On Tuesday and Wednesday, 11 and 12 July 1899, the Royal Horticultural Society held an "International Conference on Hybridisation (the Cross-Breeding of Species) and on the Cross-Breeding of Varieties" at Chiswick and London. Volume 24 of the Society's "Journal" consists of the report of the conference. Thus we have the opinions of many of the world's outstanding plant hybridizers immediately before Mendel changed their science. Most of the articles in the journal describe the results of crosses but Bateson gave a more theoretical talk. This is part of what he had to say (Bateson, 1900*a*):

> What we first require is to know what happens when a variety is crossed with its *nearest allies.* If the result is to have a scientific value, it is almost absolutely necessary that the offspring of such crossing should then be examined *statistically.* It must be recorded how many of the offspring resembled each parent and how many showed the characters intermediate between those parents. If the parents differ in several characters, the offspring must be examined statistically, and marshalled, as it is called in respect of each of those characters separately.

It is almost as though Bateson is advising a graduate student, by the name of Mendel, how to plan his Ph.D. research program!

There are many aspects of the story about Mendel that may be of interest to students. One is the almost universal attention that is given to the scientist who makes the discovery. Until recently scientists, especially biologists, could hardly expect to "make their fortune" as scientists—that is, a big $$ fortune. The rewards to a scientist come from the joy of probing nature for her regularities and the approval of one's peers for research well done and for formulating bold and imaginative hypotheses. To this day scientists look at the Mendelian paper in awe. How could he have gone so far beyond the existing paradigm and made observations that were, well after his death, to revolutionize the biological sciences?

Another interesting point for students is that, time and time again, it seems that when the field is "ready" the discovery will be made. If Mendel had never lived, the history of genetics would not have been greatly different. About the year 1900 someone or another would have reached similar conclusions. It just happened that it was de Vries and Correns. Tschermak was so close that he is usually included with de Vries and Correns as a codiscoverer. In a year or so Bateson might have independently discovered the Mendelian rules for inheritance. There seems to be an element of inevitability in the progress of science.

Initial opposition to Mendelism

In the telling of the Mendelian story, students may be led to believe that in 1900, with the publication of the papers of de Vries and Correns, "pure science" had finally triumphed. Not at all. There was vigorous, at times vitriolic, opposition to Mendel's conclusions (Provine, 1971). This scientific donnybrook mainly involved three Englishmen—William Bateson *vs.* Karl Pearson and W. F. R. Weldon, each side with a camp of followers. The two schools were fundamentally different in their approaches. Bateson sought information about inheritance from experimental crosses. Weldon, Francis Galton, and Karl Pearson sought to apply mathematical, and especially statistical, methods to biological problems. The opposition of these biometricians is all the more surprising when we remember that Mendel had relied so heavily on mathematics.

The basic dispute began before 1900 and had to do with evolution. Once again it was a case of conflicting paradigms. Weldon, Galton, Pearson and others followed Darwin in believing that evolution is based on gradual phylogenetic changes. In natural populations the variation seems to be continuous. When arranged by size or essentially any other characteristic the individuals in a species seem to show continuous variation. Not surprisingly it was assumed that evolution involves changes so minute that, only with the passage of long intervals of time, would one observe any difference.

An important statement of this continuous variation school was Galton's Law of Ancestral Heredity. He viewed inheritance in its totality and pointed out that each individual's hereditary characteristics seem to come from not only from the parents but also from more remote ancestors. On the basis of a careful study of the pedigrees of Basset hounds, Galton (1897) proposed his famous law.

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> The law to be verified may seem at first sight too artificial to be true, but a closer examination shows that prejudice arising from the cursory impression is unfounded. This subject will be alluded to again, in the meantime the law shall be stated. It is that the two parents contribute between them on the average one half, or (0.5) of the total heritage of the offspring; the four grandparents, one quarter, or $(0.5)^2$; the eight great-grandparents, one eighth, or $(0.5)^3$, and so on. Thus the sum of the ancestral contribution is expressed by the series $\{(0.5) + (0.5)^2 + (0.5)^3, \&\}$, which, being equal to 1, accounts for the whole heritage.

Thus, a trace of even our most remote ancestors is found in ourselves and this past heritage would put a brake on sudden changes. The Darwinian demands for a mechanism for slow and imperceptible changes in evolution would be satisfied.

But how could Galton's Law work? Today our minds are so fixed with the notion that our genes come only from our parents, roughly half from each, that we cannot imagine a mechanism for inheritance from venerable ancestors that seems to bypass parents. The answer is that Galton was talking about phenotypes, not genotypes. It was, and still is, well known that phenotypic characteristics may be expressed in an individual whereas they were not expressed in the parents.

This notion of continuous variation in evolution and, of course, inheritance, was challenged by Bateson and others. He had been a student of evolution and heredity for many years. In 1894 he had produced a mammoth volume *Materials for the Study of Variation Treated with Especial Regard to Discontinuity in the Origin of Species.* He wished to discover whether the evidence suggested that evolution is based on continuous variation or discontinuous variation and concluded that the latter was possible. In 1900 he felt much the same and wrote:

> We are taught that Evolution is a very slow process, going forward by infinitesimal steps. To the horticulturist it is rarely anything of the kind . . . . It is going at a gallop. Whenever, then, it can be shown that a variation comes discontinuously into being, it is no longer necessary to suppose that for its production long generations of selection and gradual accumulation of differences are needed, and the process of Evolution thus becomes much easier to conceive. According to what may be described as the generally received view, this process consists in the *gradual* transition from one normal form to another normal form. This supposition involves the almost impossible hypothesis that every intermediate form has successively been in its turn the normal. Wherever there is discontinuity the need for such a suggestion is wholly obviated. (1900*a*, p. 62)

No wonder Bateson found the Mendelian paradigm so acceptable. Hereditary differences could be striking; that is, variation appeared to be discontinuous. To Bateson and his followers the Mendelian model was compatible with their paradigm.

(As an aside it is of interest to note that a variant of this debate is still with us. Some evolutionists believe that the major pattern of evolution is based in small changes. Others believe the common pattern to be slow changes over long periods of time followed by short periods of rapid change—punctuated equilibria. Some of the confusion is a consequence of how large can a change be and still be small. Also, what is a long time and what is a short time? Some "short" times turn out to be about 10,000 years. The answer will probably be that some lineages are characterized by slow, relatively even, changes over the eons, others by stasis and jerks, and others with little appreciable change over very long periods of time. The two polar schools then are: Evolution by Creeps and Evolution by Jerks.)

The vehemence with which the debates raged indicated, quite clearly, that adherents to the older paradigm of continuous variation felt threatened. Yet those in the other camp who saw great promise in Mendel's approach, which supported discontinuous variation, had to admit that Mendel's conclusions could not account for the results of breeding experiments in all organisms and for all characteristics.

The consequence was that Bateson and the breeders continued to perform experiments that showed to what extent Mendel's principles could be extended, and Weldon and others continued to point out that not all could be explained on the original Mendelian hypothesis.

Weldon (1902) summarized Mendel's conclusions and wrote

> It is clearly important to test these remarkable statements by a careful study of the numerical results, and by the application of such tests as may be possible. It seems to me that by neglecting these precautions some writers have been led to overlook the wonderfully consistent way in which Mendel's results agree with his theory. (p. 232)

Weldon subjected the ratios to statistical tests and concluded that

> if the experiments were repeated a hundred times, we should expect to get a worse result about 95 times, or the odds against a result as good as this or better are 20 to 1. (p. 235)

Years later still another mathematically-inclined scientist, R. A. Fisher (1936), was to deal with the problem of Mendel's data being "too good." In any event there was abundant confirmation. Sinnott and Dunn (1925, p. 47) list the ratios found by Mendel and by six other plant breeders who attempted to check Mendel's results between 1900 and 1909. In the case of the *yellow* × *green*, for example, the total number of seeds was 179,399. Of these, 134,707 were *yellow* (75.09 percent) and 44,692 (24.91 percent) were *green*. Mendel had reported 75.05 percent *vs.* 24.95 percent. Apparently it was not all that difficult to obtain data that were "too good."

It bears repeating that Mendel never published his full data. His 1865 paper was based on lectures and it would have seemed reasonable for him to select the data from those crosses that best illustrated the hypothesis he was proposing. When giving public lectures scientists do not describe all of their experiments and give all of their data—even though it sometimes seems that they do. Then, too, Mendel was following the procedures of the 1860s, not those of today. But, when all is said and done, it has turned out that Mendel was right.

S. Wright (1966) studied the data again and concluded "I am confident, however, that there was no deliberate effort at falsification." See also Orel (1968).

Weldon went on to question the notion of dominance and recessiveness. He made the mistake, which Mendel was at pains to avoid, of assuming that the same phenotype implied the same genotype. Weldon knew of many varieties of peas that had characteristics similar to those Mendel had used. They did not always give the same results in crossing. Weldon did not seem to understand that a particular phenotype in one variety might not have the same genotypic basis as the apparently identical phenotype in another variety. In addition, Weldon did not seem to understand the importance of using parents of known constitution—whether, for example, the phenotype was produced by a homozygous or heterozygous genotype.

Nevertheless, he was able to cite cases where dominance was not complete and the "hybrids" were intermediate to some degree. This was to prove true in many cases, as Correns and others were to discover.

Weldon was attacking the notion that "Mendel's statements were universally valid" and summarizes,

> I think we can only conclude that segregation of seed-characters is not of universal occurrence among cross-bred Peas, and that when it does occur, it may or may not follow Mendel's laws. The law of segregation, like the law of dominance, appears therefore to hold for races of particular ancestry . . . . The fundamental mistake which vitiates all work based upon Mendel's method is the neglect of ancestry, and the attempt to regard the whole effect upon offspring, produced by a particular parent, as due to the existence in the parent of particular structural characters; while the contradictory results obtained by those who have observed the offspring of parents apparently identical in certain charac-

> ters show clearly enough that not only the parents themselves, but their race, that is their ancestry, must be taken into account before the results of pairing them can be predicted. (pp. 251–252)

The last objection is strange. Mendel had taken great pains to ensure that his original varieties bred true. It was one of the reasons for his success where so many others had failed. The last sentence in the quote just given shows that Weldon still thought that Galton's Law of Ancestral Heredity must be considered.

Mendelism was in clear competition with Galton's Law so, not surprisingly, the biometricians were anxious to challenge its data and conclusions—and that is what Weldon had done. Some indication of how highly this group regarded Galton is indicated by these quotations from Pearson (1898):

> In short if Mr. Galton's law can be firmly established, *it is a complete solution, at any rate to a first approximation, of the whole problem of heredity.* It throws back the question of inheritance upon two constants, which can be once and for all determined; herein lies its fundamental importance. (p. 393)

And Pearson closes his paper on this lofty note:

> At present I would merely state my opinion that, with all due reservations, it seems to me that the law of ancestral heredity is likely to prove one of the most brilliant of Mr. Galton's discoveries; it is highly probable that it is the simple descriptive statement which brings into a single focus all the complex lines of hereditary influence. If Darwinian evolution be natural selection combined with *heredity*, then the single statement which embraces the whole field of heredity must prove almost as epoch-making to the biologist as the law of gravitation to the astronomer. (p. 421)

Matters were moving very rapidly in the years 1900–1903. De Vries' (1900) "rediscovery" paper had been submitted for publication on 14 March 1900 and Corren's (1900) on 26 April. These created a great stir. Shortly thereafter Bateson (1900*b*) discussed these papers at a meeting of the Royal Horticultural Society. Subsequently a translation of Mendel's paper (Mendel, 1902) was made, thus making it readily available to the scientific world—few libraries would have possessed the original paper of 1865. Weldon's (1902) anti-Mendel paper was received by the editors of *Biometrika* on 9 December 1901.

Bateson set to work immediately and produced a book (1902), *Mendel's Principles of Heredity; A defence.* Not only does it provide a translation of Mendel's papers on *Pisum* and *Hieracium* but the data are discussed at length. The last half of Bateson's little book consists mainly in responding to Weldon's attack on Mendelism.

> At this juncture Professor Weldon intervenes as a professed exponent of Mendel's work. It is not perhaps to a devoted partisan of the Law of Ancestral Heredity that we should look for the most appreciative exposition of Mendel, but some bare measure of care and accuracy in representation is demanded no less in justice to fine work, than by the gravity of the issue. (p. 105)

Bateson then documents Weldon's errors and distortions of Mendel's work. Weldon, seeing his paradigm severely challenged, had responded in a manner we like to believe should not occur in science. He brought discredit upon himself and to the biometricians as a group. Bateson concludes as follows:

> I trust what I have written has convinced the reader that we are, [as a consequence of Mendel's work] at last beginning to move. Professor Weldon declares he has "no wish to belittle the importance of Mendel's achievement"; he desires "simply to call attention to a series of facts which seem to him to suggest fruitful lines of inquiry." In this purpose I venture to assist him, for I am disposed to think that unaided he is—to borrow Horace Walpole's phrase—about as likely to light a fire with a wet dish-clout as to kindle interest in Mendel's discov-

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> eries by his tempered appreciation. If I have helped a little in this cause my time has not been wasted.
>
> In these pages I have only touched the edge of that new country which is stretching out before us, whence in ten years' time we shall look back on the present days of our captivity. Soon every science that deals with animals and plants will be teeming with discovery, made possible by Mendel's work. The breeder, whether of plants or of animals, no longer trudging in the old paths of tradition, will be second only to the chemist in resource and in foresight. Each conception of life in which heredity bears a part—and which of them is exempt?—must change before the coming rush of facts. (p. 208)

Bateson's prediction of what might be seen ten years later was correct—Morgan would have established the groundwork for an astonishing development in genetics.

Bateson, the champion and the prophet, did much to protect and advance Mendelism in its infancy. He played a role similar to that of his countryman, Thomas Henry Huxley, who, a half-century earlier had been vigorous and effective in the defense of Darwinism.

We will return to the development of Mendelian genetics shortly but, also in 1902, a paper was published that was to unite the fields of animal and plant breeding with cytology. Thus the twin approaches to the study of inheritance were to become linked and mutually supportive—and require concordance.

SUTTON 1902: GENETICS + CYTOLOGY

Looking backwards at the conceptual development of the science of genetics, we can recognize 1902 as a year of momentous events. The young Walter Stanborough Sutton (1877–1916) was to demonstrate in a paper that year, and a second one in 1903, that there is an exact parallel in the behavior of the Mendelian hereditary units and of the chromosomes in meiosis and fertilization. The most economical hypothesis (Occam's Razor), therefore, was that the hereditary units were parts of the chromosomes. Alternatively the hereditary units might be parts of cell structures that behaved exactly like chromosomes in meiosis and fertilization.

This is obvious to us today—the unfailing clarity of hindsight. It was far from clear in 1902. The most prominent geneticist of the day, William Bateson, failed to be convinced by Sutton's data and analysis—in fact it was years before he became even partially convinced that genes *are* parts of chromosomes. E. B. Wilson, surely one of the world's outstanding cytologists, had great difficulty in understanding what Sutton was proposing. This is especially surprising since Sutton was working in Wilson's laboratory at Columbia University at the time. "Especially surprising" since we tend to think that the time of discovery is the time the significance of the discovery is understood by the scientific community. This is almost never so—it takes a long time for the "obvious" to become obvious.

Permanence and individuality of chromosomes?

Two of the premises of Sutton's hypothesis were that chromosomes persist in some form during the nuclear cycle, that is, they can be regarded as permanent structures and, furthermore, that chromosomes have individuality (that is, as we now realize, each pair of homologous chromosome has a unique cluster of genes).

In 1902 these premises had not been established beyond a reasonable doubt. The "disappearance" of the chromosomes at the time when the nucleus of a just divided cell entered the resting stage presented a serious problem for those who believed in the permanence and individuality of chromosomes. The most obvious interpretation was that chromosomes were temporary structures—a phenomenon of the mitotic period. Others believed that as the chromosomes entered the resting stage they joined, end to end, to form a continuous spireme. The spireme was thought to fracture into chromosomes at the onset of the next mitotic division. But need it fracture at the same place each mitotic division and, hence, maintain the individuality of chromosomes?

In the second edition of E. B. Wilson's *The Cell* (1900, pp. 294–304) there is strong support for the hypothesis of some type of permanence and individuality of the chromosomes. He notes that Rabl's observations, made in 1885, were evidence that

> *the chromosomes do not lose their individuality at the close of division, but persist in the chromatic reticulum of the resting nucleus.*

(The italics are Wilson's.) Wilson cites the studies of Boveri, van Beneden, and others on *Ascaris* as demonstrating that

> *whatever be the number of chromosomes entering into the formation of a reticular nucleus* [*i.e.*, a resting nucleus], *the same number afterward issues from it.*

The best evidence for this was again from *Ascaris.* At the end of telophase the nuclear membrane forms lobes that surround the ends of the chromosomes. These lobes persist and

> at the succeeding division the chromosomes reappear exactly in the same position, *their ends lying in the nuclear lobes as before* . . . . On the strength of these facts Boveri concluded that the chromosomes must be regarded as "individuals" or "elementary organisms," that have an independent existence in the cell. Boveri expressed his belief that "we may identify every chromatic element arising from a resting nucleus with a definite element that entered into the formation of that nucleus, from which the remarkable conclusion follows *that in all cells derived in the regular course of division from the fertilized egg, one-half of the chromosomes are of strictly paternal origin, the other half maternal.*"

Wilson was assembling evidence to make a point but, he noted, many cytologists did not accept this hypothesis. It is interesting for us to note today how slim the evidence may be at first for some truly basic concept—those lobes on the nuclear membrane of *Ascaris* being about the best evidence for the persistence of chromosomes during the resting stage. (During the late 1930s, when I was being taught cytology by Wilson's student and successor at Columbia University, Franz Schrader, those bumps on the *Ascaris* nucleus were *still* the prime evidence.)

In the third edition of *The Cell* Wilson (1928) notes that convincing (to some) evidence for chromosomal constancy was not available until 1901:

> That the chromosomes may show differences of sizes and shape in the same species was noted by Flemming, Strasburger and other earlier observers, but it did not at first occur to cytologists that such differences were other than fortuitous variations or fluctuations. Montgomery [1901] recognized the constancy of the differences of the chromosomes in respect to size and shape and in some cases also of behavior. His work in this field, carried out especially on the germ-cells of insects, formed the morphological counterpart of Boveri's [1902, 1907] epoch-making experimental demonstration of the physiological and qualitative differences of the chromosomes and thus contributed in an important way toward the demonstration of the genetic continuity of the chromosomes and the cytological explanation of Mendel's law. (p. 834)

The chromosomes of Brachystola

Sutton's 1902 paper was a study of the chromosomes in the testis of a grasshopper of the genus *Brachystola.*

> The chromosomes of *Brachystola,* like those of many amphibia, selachians and insects and certain flowering plants, exhibit a chromosome group, the members of which show distinct differences in size. Accordingly, one feature of [my] study has been a critical examination of large numbers of dividing cells (mainly from the testis) in order to determine whether, as has usually been taken for granted, these differences are merely a matter of chance, or whether, in accordance with the view recently expressed by Montgomery [1901], in regard to a certain pair of elements in the nuclei of one of the Hemiptera, characteristic size-relations are a constant attribute of the chromosomes individually considered.

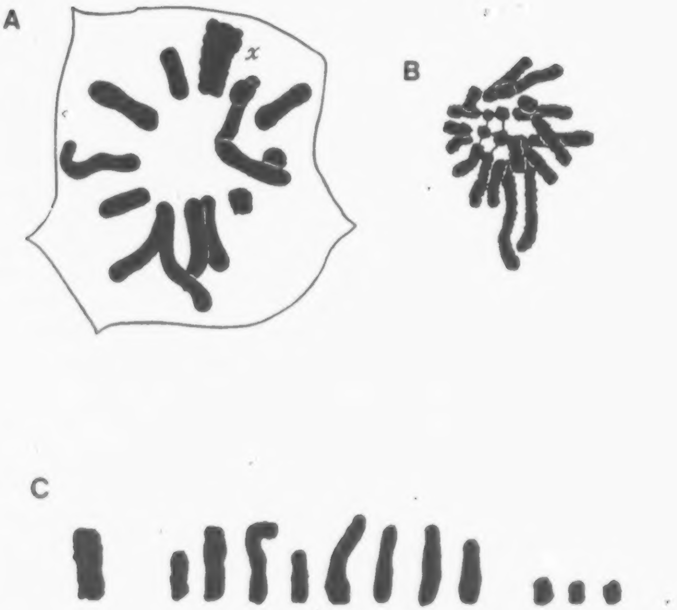


FIG. 15. Sutton's illustrations of *Brachystola* chromosomes. A shows the monoploid set of the male, B the diploid set of the female, and C are the chromosomes of A arranged by size. (A and B are from Sutton, 1920.)

> With the aid of camera drawings [*i.e.*, with a camera lucida] of the chromosome group in the various cell-generations, I will give a brief account of the evidence which has led me to adopt the latter conclusion. (p. 24)

Sutton's epoch-making analysis needed only two additional pieces of information: that chromosomes are permanent cell structures and that they are individually-specific cell structures (that is, each one is genetically different and not, as Weismann thought, each having all of the hereditary information). How was one to tell? He was working at a time long before it was possible to study the fine structure of chromosomes. The material dealt with was the deeply-stained, visually solid, chromosomes in mitosis or meiosis. The only practical means of identification was chromosomal size. Even this was beset with problems since the chromosomes change in size during mitosis, beginning as long delicate threads in prophase and becoming short and thick by metaphase. His solution was to use relative sizes, since the chromosomes seemed to change their sizes synchronously.

The spermatogonial cells in the testis of *Brachystola* undergo a series of mitotic divisions before the onset of meiosis. The youngest spermatogonia have 23 chromosomes. One of these is the so-called "accessory chromosome" that had been observed in other species and was something of a puzzle. Neglecting the accessory chromosome for a moment, camera lucida drawings showed that there were 22 other chromosomes of various sizes and shapes. When Sutton measured these carefully he found that there were not 22 different sizes but only 11. In other words there were 11 pairs of chromosomes, the chromosomes of each pair being of the same size (Fig. 15).

Whereas it was not easy to identify individual chromosomes, it was possible to recognize that the 11 pairs consisted of 8 large pairs and 3 small pairs. Careful study showed that the spermatogonia went through eight mitotic divisions and in the metaphase of each there were 8 large and 3 small pairs of chromosomes. This was the evidence that Sutton accepted as indicating that the 22 chromosomes of *Brachystola* were of 11 kinds.

Meiosis and fertilization in Brachystola

The spermatogonia then differentiate into spermatocytes that undergo meiosis. The chromosomes of the same size synapse in pairs forming 11 tetrads—8 large and 3 small. After the second meiotic division each spermatocyte will have 1 each of the 8 long and 1 each of the 3 short chromosomes.

The upper left drawing of Figure 15 shows the monoploid number of chromosomes after the second meiotic division. The drawing below is of metaphase chromosomes showing the accessory at the left and the 8 long and 3 short chromosomes to the right.

The cells of the female were not as easy to study. Sutton reported, however, that the female had 22 chromosomes—again consisting of 8 pairs of long and 3 pairs of short chromosomes. The upper right drawing of Figure 15 is of the diploid set of chromosomes in an ovarian follicle cell.

The fact that both male and female nuclei have the same 8 pairs of long and 3 pairs of short chromosomes, was additional evidence for the specificity of chromosomes. Sutton was proposing that the size differences were real and not "as usually has been taken for granted, these differences are merely a matter of chance."

Thus it seemed that the diploid number for the male was 11 pairs plus the accessory and the female had only the 11 pairs. (Sutton made an error. Later workers found that the female has 24 chromosomes consisting of the 8 long pairs, 3 short pairs, and a pair of accessory chromosomes). The year before McClung (1901) had suggested that the X might be involved in the determination of maleness, a subject to which we shall return.

According to Sutton's observations, the mature ova of *Brachystola* would, therefore, have a monoploid number of 11 chromosomes. The sperm would be of two sorts, half would have the 11 chromosomes only and half would have 11 plus the accessory. Fertilization would result, therefore, in two sorts of offspring. Some would have 22 chromosomes, and be females, and others would have 22 chromosomes plus the accessory, and be males.

Analysis of the data

What does it all mean? Here is part of Sutton's extraordinary analysis:

> Taken as a whole, the evidence presented by the cells of *Brachystola* is such as to lend great weight to the conclusion that a chromosome may exist only by virtue of direct descent by longitudinal division from a preexisting chromosome and that the members of the daughter group bear to one another the same respective relations as did those of the mother group—in other words, that the chromosome in *Brachystola* is a distinct morphological individual.
>
> This conclusion inevitably raises the question whether there is also a physiological individuality, *i.e.*, whether the chromosomes represent respectively different series or groups of qualities or whether they are merely different-sized aggregations of the same material and, therefore, qualitatively alike.
>
> On this question my observations do not furnish direct evidence. But it is *a priori* improbable that the constant morphological differences we have seen should exist except by virtue of more fundamental differences of which they are an expression; and, further, by the unequal distribution of the accessory chromosome we are enabled to compare with developmental possibilities of cells containing it with those of cells which do not. Granting the normal constitution of the female cells examined and the similarity of the reduction process in the two sexes, such a comparison must show that this particular chromosome does possess a power not inherent in any of the others—the power of impressing on the contained cell the stamp of maleness, in accordance with McClung's hypothesis.
>
> The evidence advanced in the case of the ordinary chromosomes is obviously more in the nature of suggestion than of proof,

> but it is offered in this connection as a morphological complement to the beautiful experimental researches of Boveri [we will get to them shortly] already referred to. In this paper Boveri shows how he has artificially accomplished for the various chromosomes of the sea-urchin, the same result that nature is constantly giving us in the case of the accessory chromosome of the Orthoptera. He has been able to produce and to study the development of blastomeres lacking certain of the chromosomes of the normal series.
>
> By the normal series is here meant such a one as occurs in the nucleus of either the mature germinal products, since it has been clearly shown by the well-known work on the fertilization of enucleate egg-fragments and on chemically induced parthenogenesis, that either of the ripe germ-products possesses all the chromatin necessary for the production of a normal larva . . . .
>
> Every normal fertilized egg, therefore, as well as every cleavage-cell derived from it, must have the field of each character covered by two chromosomes—one from each parent . . . .
>
> If, as the facts in *Brachystola* so strongly suggest, the chromosomes are persistent individuals in the sense that each bears a genetic relation to one only of the previous generation, the probability must be accepted that each represents the same qualities as its parent element. A given relative size may therefore be taken as characteristic of the physical basis of a certain definite set of qualities. But each element of the chromosome series of the spermatozoon has a morphological counterpart in that of the mature egg and from this it follows that the two cover the same field in development. When the two copulate, therefore, in synapsis (the suggestion that maternal chromosomes unite with paternal ones was first made by Montgomery, 1901) the entire chromatin basis of a certain set of qualities inherited from the two parents is localized for the first and only time in a single continuous chromatin mass; and when in the second spermatocyte division, the two parts are again separated, one goes entire to each pole contributing to the daughter-cells the corresponding group of qualities from the paternal or the maternal stock as the case may be.
>
> There is, therefore, in *Brachystola* no qualitative division of chromosomes but only a separation of the two members of a pair which, while coexisting in a single nucleus, may be regarded as jointly controlling certain restricted portions of the development of the individual. By the light of this conception we are enabled to see an explanation of that hitherto problematical process, synapsis, in the provision which it makes that the two chromosomes representing the same specific characters shall in no case enter the nucleus of a single spermatid or mature egg.
>
> I may finally call attention to the probability that the association of paternal and maternal chromosomes in pairs and their subsequent separation during the reducing division as indicated above may constitute the physical basis of the Mendelian law of heredity. To this subject I hope soon to return in another place.

And so he did the following year, in 1903, in an even more remarkable paper, *The Chromosomes in Heredity.*

SUTTON 1903

Sutton's (1903) paper discusses the significance of what he and others were finding out about chromosomes. If one accepts his interpretation of the nature of chromosomes and their behavior in meiosis and fertilization, there is a striking resemblance between the behavior of chromosomes as determined by cytologists and the behavior of the Mendelian units. Compare, for example, Figure 12 with Figures 13 and 14. It was assumed that segregation and recombination of the hereditary units occurred during the formation of the gametes. At this same time the chromosomes were undergoing those seemingly inexplicable maneuvers of meiosis.

The basic conclusions that can be drawn from Sutton's study of the chromosomes in *Brachystola* are (as modified from his paper):

1. The diploid chromosome group consists of two morphologically similar chromosome sets. Every chromosome type is represented twice or, as we say today, chromosomes are in homologous pairs. Strong grounds exist for the belief that one set is derived from the father and one set from the mother at the time of fertilization.
2. Synapsis is the pairing of homologous chromosomes.
3. Meiosis results in a gamete receiving only one chromosome from each homologous pair.
4. The chromosomes retain their individuality throughout mitosis and meiosis in spite of great changes in appearance.
5. The distribution in meiosis of the members of each homologous pair of chromosomes is independent of that of each other pair. While each gamete receives one of each pair, *which one* is a matter of chance.

Sutton proposed the hypothesis that Mendel's results could be explained if the hereditary units were parts of chromosomes. Figure 16 shows how this is possible.

Let us assume that Mendel's *round* and *wrinkled* alleles are on one pair of homologous chromosomes, as shown in Figure 16. Let us further assume that *yellow* and *green* are on a different pair of homologous chromosomes. A cross of *round-yellow* × *wrinkled-green* will be made (as in Fig. 14).

When meiosis occurs the gametes of the *round-yellow* parent will receive one of each of the homologous chromosomes and have the genotype **RY**. The *wrinkled-green* parent will form **ry** gametes. All individuals in the F_1 will have the same genotype, namely, **RrYy**.

Meiosis in the F_1 will result in the segregation and independent assortment of the four chromosomes, each gamete receiving one or the other member of each pair. Thus one would expect four types of gametes, **RY**, **Ry**, **rY**, and **ry**. Furthermore, the meiotic divisions would have resulted in equal proportions, 25 percent, of each.

Since the four genotypic classes of gametes are produced in equal proportions, we can use a genetic checkerboard to derive the F_2 generation. The result is a 9:3:3:1 ratio.

Thus the strict parallel between the genetic and the cytological data supported Sutton's hypothesis that Mendel's units of inheritance are parts of chromosomes.

Sutton's model, as diagrammed in Figure 16, provided a formal explanation of the major Mendelian assumptions. For example, the problem of the "Purity of the Gametes" was solved if the hereditary units are parts of chromosomes. Thus, when gametes are formed in the F_1, normal meiotic divisions would prevent two homologous chromosomes from going to the same gamete. There could be no F_1 gametes with **R** and **r** or **Y** and **y**, for example.

The chromosomal movements in meiosis also account for segregation—the **R** going to one gamete and the **r** to another. If the pairs of homologous chromosomes move to the poles of the spindle independently of each other, we have also an explanation of independent assortment. Sutton did not know whether or not this was so. In this case the data of genetics helped the cytological analysis: if the hereditary units are parts of chromosomes and, if the hereditary units assort independently, the chromosomes must assort independently as well.

As noted before, the data cannot be regarded as absolute proof that genes are parts of chromosomes. Genes could be part of some other unknown cell structure that behaves in the same way as chromosomes in mitosis, meiosis, and fertilization. When a scientist is confronted with alternative hypotheses, one involving known factors and the other involving unknown factors, common sense suggests that the hypothesis involving known factors be the basis of the research program. It would be more efficient to make observations and design experiments to test the role of chromosomes in inheritance than to first search for any unknown cell structures with chromosomal-like behavior. In any event the continued testing of deductions from the

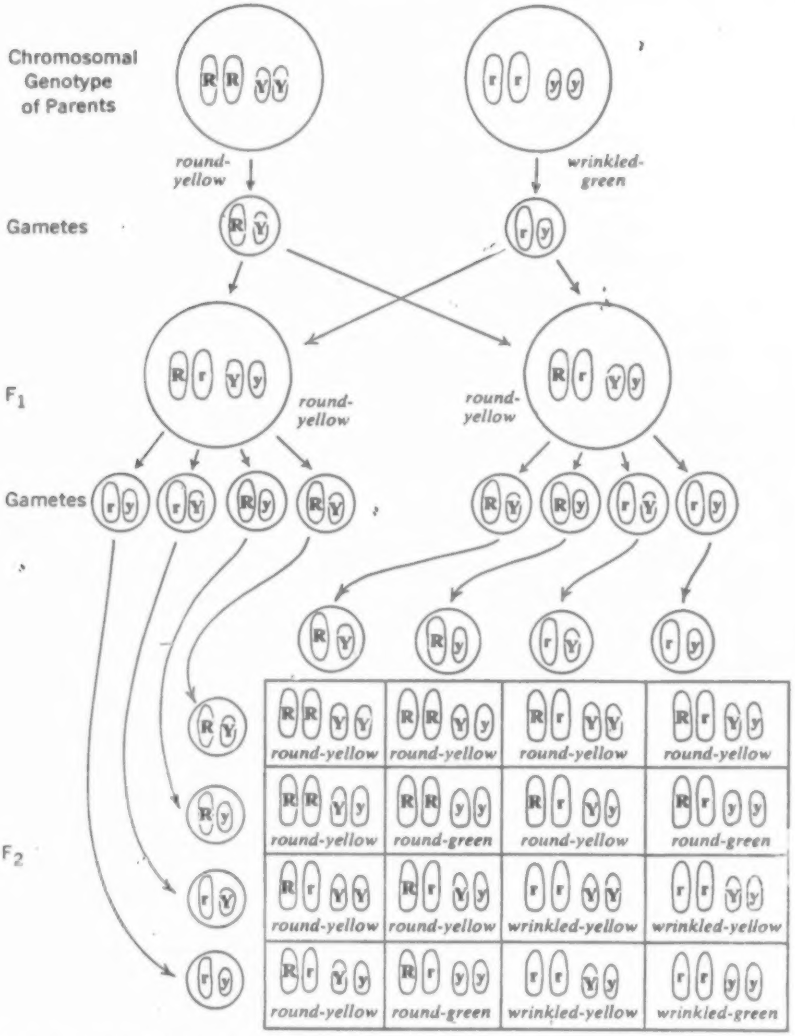


FIG. 16. The distribution of hereditary factors if they are parts of chromosomes. Compare with Figure 14.

genes-are-parts-of-chromosomes hypothesis would soon tell the experimenter whether or not a fruitful course was being followed.

The elegance of Sutton's analysis must not make us forget that it was but another step in the long and difficult research that established that the nucleus, or some part of it, is the physical basis of inheritance. Nearly 40 years had passed since Haeckel's lucky guess and nearly 20 years since the support of the hypothesis by Hertwig, Strasburger, Kölliker, and Weismann.

We may note also that by the early 1900s the number of scientists in the United States who were becoming world-class was increasing rapidly. In fact, genetics was soon to become an American science.

Deductions from Sutton's hypothesis

Sutton had formulated a hypothesis that was useful; that is, it was specific enough to permit testable deductions. If we are to use the genes-are-part-of-chromosomes hypothesis, it will be necessary to find a parallel between all types of genetic behavior and chromosomal behavior. Any variation in chromosomal phenomena from the usual condition must be reflected in the genetic results. Similarly, if genetic ratios are obtained that cannot be explained in Mendelian terms, one must find a chromosomal basis for the deviation.

Some of the deductions have been mentioned earlier. Here is a summary. We will first assume the correctness of what Sutton had to say about chromosomes, including that each chromosome can have only one allele of a contrasting pair, and what Mendel had to say about inheritance. Thus the segregation of the different alleles, **Aa** for example, must mean that there is a segregation of the meiotic chromosomes as well. There is. Furthermore, that seemingly inexplicable fact that the gametes are "pure," that is, can have only one allele of a contrasting pair, means that only one member of a pair of homologous chromosomes can enter a gamete. Cytological observations strongly suggested that this is so. In a similar manner, the independent assortment of alleles could be accounted for by the independent assortment of chromosomes at anaphase of the second meiotic division. This, however, was only probable and would remain so until it became possible to distinguish between the members of a homologous pair of chromosomes. Sutton concludes (his italics) (1903, p. 237):

> *Thus the phenomena of germ-cell division and of heredity are seen to have the same essential features, viz., purity of units (chromosomes, characters) and the independent transmission of the same*; while as a corollary, it follows in each case that each of the two antagonistic units (chromosomes, characters) is contained by exactly half of the gametes produced.

The deductions so far mentioned could be tested because both the cytological and the genetic data were available. Sutton went on to deduce that non-Mendelian results must be expected to occur if his hypothesis was correct:

> We have seen reason, in the foregoing considerations, to believe that there is a definite relation between chromosomes and allelomorphs or unit characters but we have not before inquired whether an entire chromosome or only part of one is to be regarded as the basis of a single allelomorph. The answer must unquestionably be in favor of the latter possibility, for otherwise the number of distinct characters possessed by an individual could not exceed the number of chromosomes in the germ-products; which is undoubtedly contrary to fact. We must, therefore, assume that some chromosomes at least are related to a number of different allelomorphs. If then, the chromosomes permanently retain their individuality, it follows that all the allelomorphs represented by any one chromosome must be inherited together. On the other hand, it is not necessary to assume that all must be apparent in the organism, for here the question of dominance enters and it is not yet known that dominance is a function of an entire chromosome [would you have thought of that as a problem?]. It is conceivable that the chromosome may be divisible into smaller entities (somewhat as Weismann assumes), which represent the allelomorphs and may be dominant or recessive independently. In this way the same chromosome might at one time represent both dominant and recessive allelomorphs. (p. 240)

Thus, Sutton is deducing that there must be many genes on the same chromosome and, if there are, they must be inherited together. If inherited together there would be no possibility of independent assortment and no genetic ratios of the sort found by Mendel—and by numerous other investigators by 1903. We can deduce, therefore, that an exception to the original Mendelian ratios must occur if we find more pairs of alleles than there are pairs of homologous chromosomes.

SUTTON—WILSON—MORGAN

Sutton was 25, a student with E. B. Wilson in the Zoological Laboratory of Columbia University, when he published the 1902 paper. He concluded that paper with,

> I take pleasure in expressing here my gratitude to Prof. E. B. Wilson for much valuable advice and assistance in the work upon *Brachystola* and in the preparation of the present paper.

As we have noted before, Wilson had long been interested in the possibility that the chromosomes were the physical basis of inheritance. Furthermore, he had a magisterial grasp of cytology and embryology, having already published the first two editions of *The Cell.* One of his closest friends was Th. Boveri, whose brilliant research had added so much to the knowledge of chromosomes and their possible participation in heredity. Wilson had come to Columbia from Bryn Mawr in 1891 and Thomas Hunt Morgan followed him from the same institution in 1904 (Crampton, 1942). The complex and synergistic interrelations of Wilson, Sutton, and Morgan were to climax during the following decade in the work with *Drosophila.*

Once again, however, we will note the extraordinary difficulty for those scientists, in this instance Wilson and Morgan, doing their normal science in the accepted paradigm of the moment, understanding a new paradigm. A young, though brilliant, scientist with a mind not saturated with a tremendous mass of competing hypotheses and confused facts, was able to see conceptual order where the giants could not.

E. B. Wilson describes how Sutton explained his hypothesis.

> I well remember when, in the early spring of 1902 [Sutton's first paper was in the December 1902 *Biological Bulletin* and the second in the April 1903 issue], Sutton first brought his main conclusions to my attention, by saying that he believed he had really discovered "why the yellow dog is yellow." I also clearly recall that at that time I did not at once fully comprehend his conception or realize its entire weight.
>
> We passed the following summer [1902] together in zoological study at the sea side, first at Beaufort, N.C., later at South Harpswell, Me., and it was only then, in the course of our many discussions, that I first saw the full sweep and the fundamental significance of his discovery. Today the cytological basis of Mendel's law, as worked out by him, forms the basis of our interpretation of many of the most intricate phenomena of heredity, including the splitting up and recombination of characters in successive generations of hybrids, the phenomena of correlation and linkage, of sex and sex-linked heredity and a vast series of kindred processes that were wholly mysterious before their solution was found through Mendel's law. Subsequent to the appearance of Sutton's papers, Boveri stated, 1904, that at the time they were published he had himself already reached the same general result. This does not, however, in the smallest degree detract from Sutton's fine achievement, which will take its place in the history of biology as one of the most important advances of our time. He made an indelible mark on scientific progress, and his name is known wherever biology is studied . . . .
>
> During this summer Sutton had fully worked out his theory of the chromosomes in relation to Mendel's law and upon his return to New York he immediately set about the preparations for its publication. His first paper, as already stated, appeared late in 1902, the second early in the spring of the following year. These two brief papers were intended to be of a preliminary nature, a fuller presentation of his conclusions, together with a larger number of beautiful drawings, already finished at that time, being reserved for a later work which he had expected to offer as a dissertation for the Ph.D. degree at Columbia. It was a source of profound regret to us that circumstances prevented the realization of that plan and brought his cytological investigations to a close. In spite of his brilliant talents as an investigator it would perhaps be more accurate to say because of them—the career of a teacher did not tempt him. Could he have been assured of a reasonable means of support from a life devoted to pure research, he would

> not, I believe, have hesitated. But he had to make his own way in the world and from the first had a strong inclination towards the study of medicine. The combination of circumstances proved irresistible; and after a year or two spent in business he returned to Columbia, entered the Medical School, and graduated with the highest honors two years later.

Wilson's remarks are from a memorial volume published in 1917 (Sutton, 1917). After a distinguished career as a physician, Sutton died at the age of 39. In this brief life in biological research he had produced two papers that probably can stand with those of Mendel and Watson and Crick in fundamental importance and in the brilliance of the analysis.

But once convinced, Wilson became a strong advocate. Whereas before 1900, most of his work had been in developmental biology, thereafter his research was almost exclusively in chromosomal cytology.

The clarity and explanatory ability of Sutton's hypothesis did not mean that it was immediately accepted. Far from it. According to Darlington (1960) as late as the mid-1920s in England,

> Seven men might have been willing to assert their belief in the chromosome theory [of heredity] and give their reasons for it. But against this view there were seven hundred who held a contrary opinion.

The interval between the time some important concept in science becomes true beyond all reasonable doubt to the discoverer and a few cognoscenti and its acceptance by a majority in the scientific community tended to be long in the years before World War II. It is often much shorter now that there are so many more scientists working on the same problems and progress is so rapid.

BOVERI: ABNORMAL CHROMOSOMES = ABNORMAL DEVELOPMENT

It has been mentioned before that cytology at the turn of the century was largely a descriptive science. To be sure one could treat cells with various chemical reagents and differentially stain some of the cell structures. It was not practical at that time for those testing the hypothesis that the physical basis of inheritance resides in the chromosomes to proceed as follows: If the hypothesis is true, the removal of individual chromosomes should result in some change in the organism.

Nevertheless, Boveri (1902 and especially 1907) found a way to accomplish this feat. For more than a generation the eggs and embryos of echinoderms had been studied by cytologists and embryologists and it was known how to obtain their eggs and sperm artificially. Earlier investigators had observed that if concentrated sperm are used to fertilize eggs, two sperm may enter the same egg. Each sperm brings in a division center (centrioles and centrosome) that divides. Thus there are four division centers, which form a square in the egg. Spindle fibers extend from the centers not only along the sides of the square but also across the cell to centers at the opposite corners. The chromosomes are apportioned in a most abnormal manner to the first four cells that result from the first division.

Boveri realized that here was a procedure for altering the set of chromosomes that a cell receives.

The diploid number of chromosomes is 36 in the species of sea urchin that he used. They are small and apparently uniform. There was no *a priori* reason to assume that the individual chromosomes might differ from one another. Recall that Weismann had suggested that each chromosome has all of the hereditary information. Nevertheless Boveri sought to test the hypothesis that the chromosomes differed from one another and a full set of 36 would be necessary for normal development.

In a normal monospermic zygote the 36 chromosomes would replicate before first cleavage to form 72 chromosomes and these would be divided equally at the mitotic first division with 36 going to each daughter cell. Mitotic divisions throughout development would maintain this number.

Since the monoploid number of chromosomes is 18, the dispermic embryo would have 54, that is, 18 each from the two sperm pronuclei and 18 from the egg pronucleus. Each chromosome would replicate before first cleavage to produce 108. The embryo would then undergo the atypical first division that results in four cells. There is no way that each of these four cells can receive the normal complement of 36 chromosomes: 108 if divided equally among the four would give each cell 27. Furthermore, examination of fixed and stained cells showed that the distribution of chromosomes among the four cells was most uneven.

Thus, if each cell must have the normal complement of 36 chromosomes for development to be normal, these dispermic eggs would be expected to develop abnormally. They did—out of 1,500 embryos, 1,499 were abnormal. (That normal one could have been experimental error.)

Boveri found that if the dispermic eggs were shaken, one of the division centers might not divide. The result would be three division centers, arranged in a triangle with spindles between. Such an embryo would divide into three cells at first division. Again the chromosomes were divided irregularly but, in this case, there would at least be a *chance* that each cell could receive a normal set of 36 chromosomes—if the total of 108 is divided by 3, the result is 36. Of 719 embryos of this sort, 58 developed normally.

According to Boveri, these data correspond fairly well with the chance expectations that each cell will receive the normal set of chromosomes and so the embryo can develop normally.

The conclusion was, therefore, that every cell in the embryo must have the normal set of 36 chromosomes if the development is to be normal. This must mean that each chromosome in the set is endowed with a specific quality in spite of the fact that morphologically all appear to be identical.

A COMPARISON OF SUTTON'S APPROACH WITH BOVERI'S APPROACH

Sutton and Boveri had used entirely different methods to reach a similar conclusion: chromosomes are the physical basis of inheritance. They had not shown, of course, that chromosomes are the only bearers of hereditary information.

Sutton's hypothesis relating genes and chromosomes was made and tested without his ever seeing a gene, let alone seeing a gene as part of a chromosome. He related gene and chromosome because they behaved in an apparently identical manner in meiosis and fertilization. To be sure this was indirect evidence but the discovery of causal relations in science is often based on the parallel behavior of phenomena.

Long ago the daily cycle of tides was associated with the relative position of the moon and to a lesser degree to the relative position of the sun. The relationship of moon and tides can be checked in several ways and the hypothesis so firmly established that one can predict, with a high degree of accuracy, the tides in the future. Parallel behavior is the only practical way to study the relation of moon and tide. One cannot perform the more critical experiment of excising the moon from the solar system and noting the consequences.

Correlations need not, however, always denote a causal relation. The 28 day lunar cycle and the 28 day menstrual cycle of the human person were long suspected to be causally related but we have no convincing evidence for such a causal relation.

Boveri performed a more direct test of the relation between chromosomes and inheritance by altering the chromosomes and studying the consequences.

Which method is superior, the direct of Boveri or the correlative of Sutton? So far as supporting the hypothesis is concerned the two are about equal. Beyond that there is a large and important difference. What would be the next step in Boveri's approach? It is hard to see how deeper insights into the nature of inheritance could have been obtained with the methodology of the time. One might think of removing individual chromosomes but not only was the methodology unavailable but also there was no way of distinguishing one chromosome from another in the sea urchin.

Sutton's approach, on the other hand, was far more elegant than Boveri's. He was able to link Mendelism and cytology, which of course Boveri could not, so closely as to suggest testable deductions. Sutton had set the stage for the culmination of classical genetics in the work of Morgan's *Drosophila* group a decade later. And, it is interesting to note, eventually the Morgan group was able to manipulate individual chromosomes by genetic methods.

The genes-are-parts-of-chromosomes hypothesis is sometimes called the Sutton-Boveri hypothesis (for example, Mayr, 1982, pp. 747–749) or even the Boveri-Sutton hypothesis. This is astonishing when one considers the relative contributions of the two in 1902–1903. Boveri only hinted. Sutton worked out the hypothesis and its implications brilliantly. One suspects that Boveri is listed as a co-equal more because of who he was than for what he said. And he was, indeed, a brilliant scientist with a long record of fundamental discoveries.

Sutton and, to a lesser degree, Boveri were not the only ones, in the first two years after Mendel's work became generally known, to suspect that cytology was to provide the mechanism for Mendelian inheritance. E. B. Wilson (1924), who was surely in a position to know, wrote:

> A possible connection between the Mendelian disjunction and the reduction division was suggested nearly at the same time by several observers, including Strasburger, Correns, Guyer, and Cannon. It was, however, Sutton (1902–3) who first clearly set forth in all its significance the cytological explanation of the Mendelian phenomena that is offered by the behavior of the chromosomes, and thus initiated the remarkable movement in this direction that followed. (p. 9)

That is the same Correns who was one of the first to appreciate Mendel's work. The case of W. A. Cannon is especially interesting. He was also a student at Columbia University but, whereas Sutton was in the Department of Zoology, Cannon was in the Botany Department. Cannon was studying the cytology of cotton hybrids and observed the reduction division and saw a possible relation to Mendelian inheritance.

This hypothesis was "hot property" and the question of priority was sure to arise. The two students asked Wilson to publish a short paper announcing what they had done. He did in 1902.

> Since two investigators, both students in this University, have been led in different ways to recognize this clue or explanation, I have, at their suggestion and with their approval, prepared this brief note in order to place their independent conclusions in proper relation to each other and call attention to the general interest of the subject.

Cannon's first paper appeared in December 1902—as had Sutton's. In 1903 two additional papers appeared.

Once again an important concept was "in the air." When Mendelism emerged in 1900, cytology was ready:

> Montgomery (1901), without knowledge of Mendel's fundamental law of segregation, brought together almost all of the essential data for its explanation, though he did not bring them into specific relation with the genetic phenomena. (Wilson, 1924, pp. 8–9).

Then Sutton went on to make a small evidential step and a giant conceptual contribution. But, as we have already seen, not everyone was listening.

Now is the time to return to Bateson and the breeders and observe the rapid expansion, amplification, and extension of Mendelism. Thereafter we will return to the cytologists and see how they dealt with those extra chromosomes ("accessory", "X") that Montgomery, Sutton, and others had reported.

DEFINING SOME GENETIC TERMS

In the year 1902 still another publication of fundamental importance appeared—the first of the *Reports to the Evolution Committee of the Royal Society.* This one was by Bateson and Miss Saunders (1902). In 1897 they began a series of crosses of different varieties of plants and animals. Their initial intent was to learn more about continuous and discontinuous inheritance as well as the phenomenon of "prepotence," which would later be known as dominance. At that time they thought that,

> From what had been hitherto ascertained regarding the phenomena of heredity, the inference could scarcely be avoided that no universal law obtains, but that by studying various specific cases distinct specific laws may be detected. (p. 3)

So much for Darwin, Nägeli, Weismann, and Galton! Before Bateson and Saunders published their results they realized that "the whole problem of heredity has undergone a complete revolution" (p. 4) and they were able to use the Mendelian paradigm to account for their results.

Bateson (in Bateson and Saunders, 1902) provided us with some of the basic terminology for Mendelian genetics:

> This purity of the germ-cells, and their inability to transmit both of the antagonistic characters, is the central fact proved by Mendel's work. We thus reach the conception of unit-characters existing in antagonistic pairs. Such characters we propose to call *allelomorphs*, and the zygote formed by the union of a pair of opposite allelomorphic gametes, we shall call a *heterozygote*. Similarly, the zygote formed by the union of gametes having similar allelomorphs, may be spoken of as a *homozygote*. (p. 126)

In time "allelomorph" was shortened to "allele."

At this point I will explain how I plan to use "gene," "locus," and "allele." Those with long experience in teaching genetics in introductory courses know how difficult these terms may be for students. The problem, however, is less with the competence of students and more with the inexact way geneticists use these terms. And in our time, the more we learn of the molecular basis of a gene locus, the fuzzier the gene becomes. For the moment I will ignore the present and discuss genes as they existed in the Golden Years of Classical Genetics, when they were those little round beads on a string—well, not quite.

Much of the trouble comes from the frequent use of allele and gene as synonyms. I will try not to do that but, since many of my friends are geneticists, I may slip into that error. A *gene* will be a portion of a chromosome that produces an indivisible effect (the atoms of heredity!), which must be detectable, of course (or we would never know of its existence). The position that the gene occupies on a chromosome will be its *locus*. *Alleles* will be the different detectable variations of that gene. Every gene must have at least two alleles—otherwise we would not know of its existence. A gene reveals its existence when it *mutates* in such a manner that the new mutant allele has a detectable effect.

VARIATIONS IN MENDELIAN RATIOS

The results of crossing varieties of peas—dominance and recessiveness, segregation, independent assortment with the consequences that one observed a 3:1 ratio in the F_2 of a monohybrid cross and a 9:3:3:1 ratio in the F_2 of a dihybrid cross—exhibited a high degree of uniformity and thus raised the question of the universality of these findings.

The development of this topic provides a fine opportunity for students to become involved in suggesting hypotheses and using actual data to test their hypotheses. Toward that end the following suggestions are offered.

Experience suggests that it is best to start with very simple crosses and work up to some that cannot be solved until more information is provided. Thus, students might be asked to write out schemes similar to Figures 13, 14, and 16, using the general symbols **A**, **a**, **B**, and **b** for the following situations:

1. Scheme and expectations for a simple monohybrid cross.
2. Scheme and expectations for a simple dihybrid cross.
3. Scheme and expectations should the genotype **Ab** not have the appearance of the *A-type* individual but rather of something else.
4. Scheme and expectations should a single or double dose of **A** plus a single or double dose of **B** result in a phenotype unlike either the *A-type* or *B-type* individuals. The expectations can be revealed by checking the genetic checkerboard for a dihybrid cross and scoring the expected phenotypes of the various genotypes.

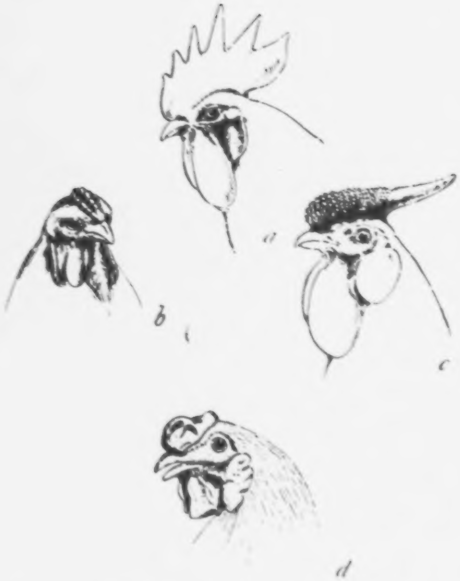


FIG. 17. Comb shape in chickens. *a* is single comb. *b* is rose. *c* is pea. *d* is walnut. (Morgan, 1919)

These four possibilities may be regarded as hypotheses. The student's problem will then be to determine which hypothesis best explains the following data.

In the first report to the Evolution Committee, Bateson and Saunders (1902) described numerous crosses, many of them begun before they knew of Mendel's work. Miss Saunders described her experiments with wild species of the genus *Lychnis*, the campion. Some of the species are *hairy* and others are *glabrous*, that is, without hairs.

a. Crosses of *hairy* × *glabrous* produced an F_1 consisting of 1006 *hairy* and 0 *glabrous*.

b. When the F_1 individuals were crossed they produced an F_2 consisting of 408 *hairy* and 126 *glabrous*.

c. When an F_1 individual was crossed with a pure breeding *hairy*, the offspring consisted of 41 *hairy* and 0 *glabrous*.

d. When an F_1 individual was crossed with a pure breeding *glabrous*, the offspring were 447 *hairy* and 433 *glabrous*.

The students should be able to deduce the possible genotypes of individuals in a, b, c, and d and, finally, summarize all the information into a diagrammatic hypothesis to explain the results.

In the same publication Bateson reported his early experiments with chickens. He studied many sorts of characteristics, including the shape of the combs that were typical of the various breeds (Fig. 17). One type was called *pea* and another *single*.

a. When *pea* was crossed with *single*, all of the F_1 had *pea* combs.

b. When the F_1 were crossed, the offspring were 332 with *pea* combs and 110 were *single*.

Again, the students should suggest the genotypes and be able to offer a genetic diagram of the crosses.

In their second report (Bateson *et al.*, 1905), Miss Saunders reported on many crosses with plants of the genus *Salvia* (mints). True breeding strains with pink and white flowers were used.

a. When *pink* is crossed with *white*, all of the F_1 are *violet*.

b. In a cross of the F_1 plants, one cross produced 59 *violet*, 25 *pink*, and 34 *white*. In another cross, there were 225 *violet*, 92 *pink*, and 114 *white*.

This situation should prove easy for your students.

Bateson reported additional experiments on the inheritance of comb shape in chickens. *Rose* comb when crossed with *single* gave all *rose* in the F_1.

a. When the F_1's were crossed with one another, the F_2 gave 221 *rose* to 83 *single*.

b. When an F_1 was crossed with a *single*, the offspring were 449 *rose* and 469 *single*.

Thus, both *rose* and *pea* are dominant to *single*. But how could there be 3 alleles: *single*, *rose*, and *pea*? The plot really thickened with a cross of pure-breeding *pea* with pure-breeding *rose*. The F_1 generation was uniform but all had a type of comb not seen in either parent. It was *walnut*, a comb shape that was known in other breeds (Fig. 17).

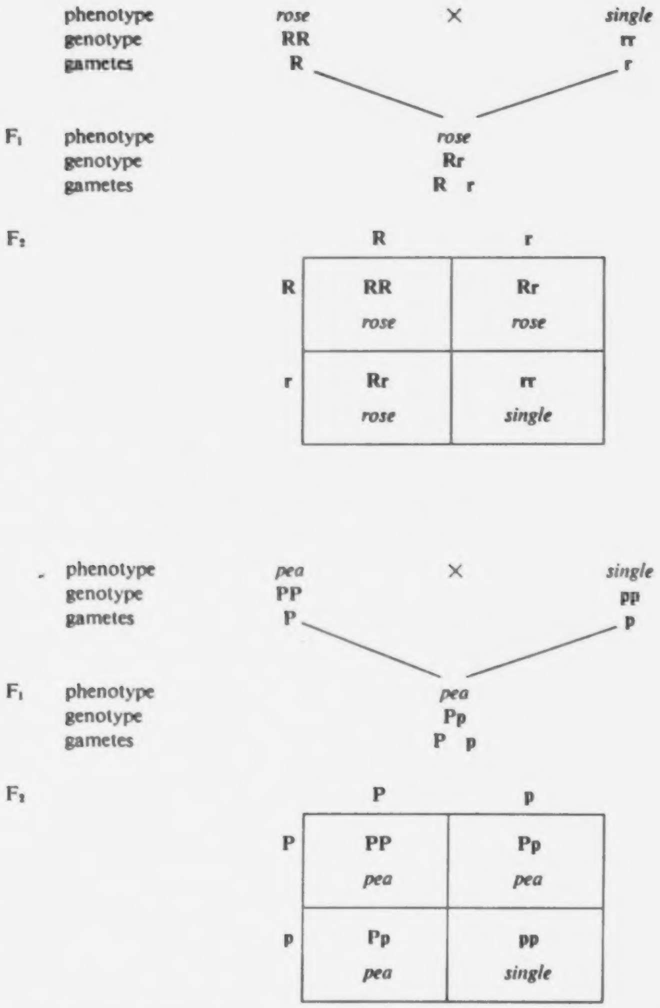


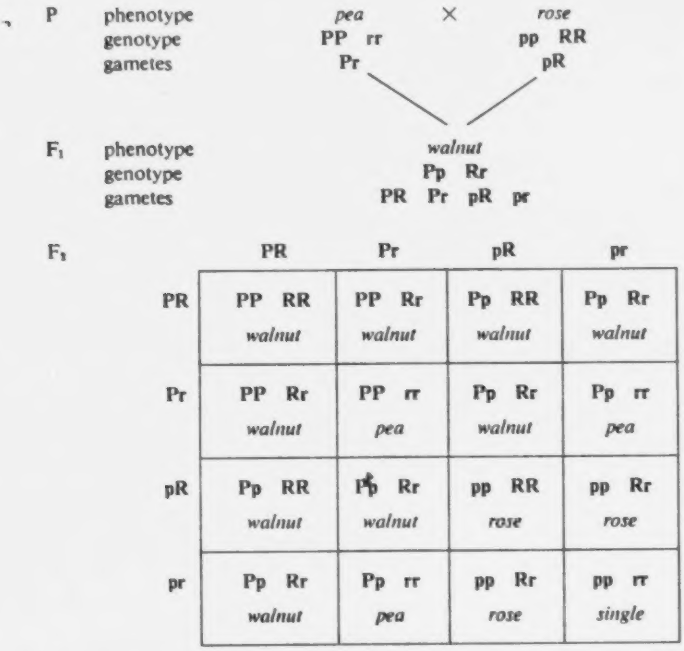
FIG. 18. Genetic diagram for crosses of chickens with different types of combs.

c. When the F$_1$'s were crossed, the F$_2$ consisted of 99 *walnut*, 26 *rose*, 38 *pea*, and 16 *single*.

d. When the F$_1$ was crossed with *single*, the offspring were 139 *walnut*, 142 *rose*, 112 *pea*, and 141 *single*.

These crosses involving comb shape may prove a real puzzle for many students but, if they have considered the hypothetical situations suggested, they will realize that the ratio is approximately 9:3:3:1 in c, meaning that two pairs of alleles are involved. These alleles are abiding by the Mendelian rules of dominance, segregation, and independent assortment. They are puzzling only because both pairs are affecting the same character—comb shape. Hopefully your students will identify the situation as that of scheme 4 and shown in Figures 18 and 19.

The following crosses represent still another variation on Mendelian ratios and it will probably be too difficult for most students. It may be useful, however, for



	PR	Pr	pR	pr
PR	PP RR *walnut*	PP Rr *walnut*	Pp RR *walnut*	Pp Rr *walnut*
Pr	PP Rr *walnut*	PP rr *pea*	Pp Rr *walnut*	Pp rr *pea*
pR	Pp RR *walnut*	Pp Rr *walnut*	pp RR *rose*	pp Rr *rose*
pr	Pp Rr *walnut*	Pp rr *pea*	pp Rr *rose*	pp rr *single*

F_2 ratio: 9 *walnut;* 3 *rose;* 3 *pea;* 1 *single.*

FIG. 19. Diagram of a cross of *pea comb* × *rose comb* chickens showing the production of *walnut.*

the better and more highly motivated students to give it a try.

Bateson and others (1906) had done numerous crosses with confusing results with both sweet peas (*Lathyrus*) and stocks (*Matthiola*).

> a. When two different varieties with *white* flowers were crossed, all of the F_1 plants were *colored.*
>
> b. When the F_1's were crossed it appeared, at first, that there were equal numbers of *white* and *colored.* Continued study showed, however, the ratio to be 9 colored to 7 white.

Figure 20 is Bateson's diagram of the F_2 results. He and his co-workers concluded that the white flower color of the two original *white* varieties was not controlled by the same genotype. One was shown as **CCrr** and the other as **ccRR**. Color requires at least one **C** and one **R**. The F_1 would all be **CcRr**, and hence colored.

These few examples of genetic crosses indicate the sorts of problems that can be given to students to solve. There are numerous others, of course. The standard textbooks of genetics have many examples: Ayala and Kiger (1984), Strickberger (1985), Suzuki, Griffiths, and Lewontin (1981). Many of the problems in these books give only the ratios observed, not the actual numbers of individuals in each phenotypic class. It will be more valuable if the students deal with the real data because they can reach an important conclusion, but when ratios alone are given that important conclusion has already been reached. If the problems range in difficulty from simple to challenging, there will be something for all. We tend to neglect the better students so it is important that there be an opportunity for them to be challenged as well.

It will be especially valuable if the students can be given an opportunity to determine, statistically, how well the actual data conform to expectations.

More problems will be given when *Drosophila* is discussed. As a concluding prob-

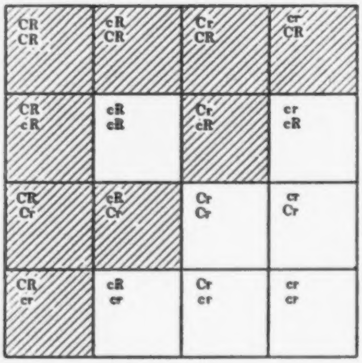


FIG. 1.—Diagram showing the nature of the ratio 9 : 7 in F_2. The character, colour for example, appears only when C and R meet. Each square is a zygote, and the lettering shows its gametic composition. The hatched squares represent coloured plants; the plain are whites.

FIG. 20. The genotypes and phenotypes of the F_2 of a cross of two different types of plants with *white* flowers. (Bateson, Saunders, and Punnett, 1906)

lem at this stage, extract from your students an answer to this: if we wish to determine the genotype for an individual with one or more different pairs of alleles, what cross will provide the most information? It is hoped that some of the students will realize that when the individual of unknown genotype is crossed to a pure recessive, the phenotypic classes of the offspring will be identical to the genotypic classes of the unknown individual's gametes. And, if we know that, it is simple to determine the genotype of the unknown individual. Thus, if we wished to determine the genotype of a *round-yellow* pea plant of unknown parentage, we could cross it with a *wrinkled-green* one. Such a cross to the pure recessive is known as a *test cross,* a term suggested by Bridges (1934). If the offspring are ¼ *round-yellow,* ¼ *round-green,* ¼ *wrinkled-yellow,* and ¼ *wrinkled-green,* the gametes of the unknown individual must have been **RY**, **Ry**, **rY**, and **ry**. Thus the unknown would have been **RrYy**.

This survey of the genetics of the first few years of the 20th century makes us acutely aware of the complexity and the confusion that existed. Those who wished the world to be as outlined for Mendel's peas were soon to find that it was not. This does not mean that the original Mendelian story was "wrong." It means only that it was incomplete and was being replaced with a deeper understanding of the nature of inheritance.

Not one of the original Mendelian rules was found to be correct for all cases. It can be argued that the remarkable progress of genetics was based on an attitude that might seem "unscientific." That is, from the time that Mendel's work became known, it was clear that the original Mendelian hypothesis did not apply to all organisms. Nevertheless, the "true believers" ignored the exceptions and slowly found what could be explained in the original Mendelian terms. As they came to know more and more about breeding experiments in different species, it became possible to expand theory to accommodate the new data. It proved possible to understand more and more of the exceptions.

It was eventually found that some of the most intractable problems had a chromosomal basis. One such problem had to do with those puzzling "accessory" or "X" chromosomes, so we should now check on what the cytologists were doing in the first few years of the 20th century.

MONTGOMERY 1901: BEGINNING TO PUT IT TOGETHER

One of the most influential cytological studies at the turn of the century was a detailed investigation of spermatogenesis and oogenesis in a variety of Hemiptera by

Montgomery (1901). The importance of the paper lies in the rich variety of material described and the fact that, in many instances, he marshalled evidence that would enable others to make important breakthroughs in theory. Both Sutton and Wilson found much of importance in Montgomery's observations and interpretations.

At the time when none of the following hypotheses were widely accepted, Montgomery interpreted his data as suggesting that chromosomes are permanent cell structures; that they exist in homologous pairs consisting of one originally inherited from the mother and the other from the father; that synapsis consists of the coming together of these homologous chromosomes; that in meiosis each spermatid receives one chromosome of each type. He described accessory chromosomes but failed to relate them to the sex determination.

The species of Hemiptera are ideal from several points of view. The chromosomes are not overly numerous, they often differ from one another structurally, and the species are easily collected. One of the most important features, however, is the organization of the testes. The immature cells are at one end and, as one passes through the organ, the various stages in spermatogenesis occur in sequence, ending with mature sperm. In a single testis, therefore, one can study the entire process and be sure of the order of the various stages.

Montgomery starts by listing the problems of interest, such as,

> the significance of the changes in the synapsis stage, the significance of the chromatin nucleoli, the reason for a reduction division, the significance of the sequence of the stages of the germinal cycle, and the question as to why different species have different numbers of chromosomes . . . .
>
> It is impossible to answer these problems by an examination of a single species, and accordingly there are presented here the results of a comparative study of the spermatogenesis of some forty-two species of Hemiptera heteroptera, belonging to twelve different families. This comparative study has brought to light certain wholly unexpected phenomena, and none less anticipated than the discovery of four species with an uneven normal number of chromosomes [these are the sex chromosomes]; this discovery has furnished facts for explaining how the chromosomal numbers may change with the evolution of the species, and how the chromatin nucleoli may have originated. And only such a comparative study could furnish facts to show that in the synapsis stage bivalent chromosomes are formed by the union of paternal with maternal chromosomes—*i.e.*, that this is the stage of conjugation of the chromosomes. The comparative method in Cytology cannot be overestimated, [t]hough of course careful detailed examinations should be carried on at the same time. For a single object is rarely capable of serving as the basis of explanations of all the problems; an investigation of a number of forms always shows that some are more favorable than others for answering certain questions, and then there is the chance that a wholly unexpected discovery may be made that may have great significance. So the plea is made here for the comparative method in Cytology . . . . (pp. 154–155)

Montgomery's remarks emphasize a very important principle of scientific investigation: more often than not one seeks specific sorts of evidence rather than considering all the evidence in an even-handed manner. If the chromosomes of one species of Hemiptera exhibited a peculiar behavior, why use this to support a hypothesis rather than those 41 species that do not? "Unscientific" as this procedure may appear, we will find that the great success of genetics was a consequence of emphasizing data that conformed to Mendel's hypothesis and ignoring that which did not. In time the exceptions came to be understood and incorporated into genetic theory.

One might liken the conceptual development of genetics to the formation of a crystal in a super-saturated solution. The ions in solution are the unorganized facts about chromosomes, breeding data, and much of biology. A tiny crystal, the working hypothesis, begins to form and gradually all those randomly distributed ions become incorporated in an organized whole.

Montgomery was 28 when his classic paper was published. He was almost the same age as Sutton. Both died before they were 40.

THE DISCOVERY OF SEX CHROMOSOMES

As Montgomery had suggested in his 1901 paper, just quoted, it is important to study a variety of organisms since some may show variations in the behavior of their chromosomes and this will provide data not otherwise available and conclusions not otherwise possible. The accessory chromosomes turned out to be a case in point. In fact, it was by studying their behavior that the critical evidence that genes are parts of chromosomes was eventually obtained.

Recall the reason that Boveri experimented with polyspermy in sea urchins. His system provided a mechanism for allocating abnormal groups of chromosomes to the cells of the early embryo. As a consequence, the embryos died and the hypothesis that a set of normal chromosomes is necessary for normal development was supported.

Nevertheless, this was not a fruitful type of experimentation. There was no means of recognizing individual chromosomes, of relating specific chromosomes to specific phenotypes, or of controlling which chromosomes entered which cell.

As it so often happened, nature was doing the required experiment all along. And as it so often happens, it took a considerable length of time for cytologists to realize that was so.

In 1891 H. Henking published his observations on the behavior of chromosomes in spermatogenesis in the bug, *Pyrrhocoris* (Fig. 21). This species has a diploid number of 23 chromosomes—11 pairs plus an extra one, which he called the "X." At synapsis the 11 homologous pairs formed 11 tetrads. But the behavior of the **X** was different. Having no homologue it could not synapse but it replicated to form a dyad-like structure. At the beginning of meiosis, therefore, the cell would have 11 tetrads plus the **X** in the form of a dyad. At the first meiotic division the 11 tetrads separated, a dyad from each going to each daughter cell. The **X**-dyad, however, went entirely to one pole of the spindle and, hence, was included in only one of the daughter cells.

At the second meiotic division of the cell with only the 11 dyads, separation of the dyads was observed and one chromosome of each went to each daughter cell. The cell with the 11 dyads plus the **X**-dyad divided and one chromosome of each of the 11 dyads went to opposite poles of the spindle. The **X**-dyad divided also and each of the daughter cells received one **X** chromosome.

Thus, of the four cells produced by meiosis, two would have 11 chromosomes and two would have 11 chromosomes plus an **X**. Therefore two types of sperm would be formed, one type with an **X** and the other without.

Henking reported what he had seen and left it at that. Thereafter other observations were made on species that had these peculiar chromosomes. They were noticed either because they stained differently from the other chromosomes, or they might move to the poles of the spindle earlier or later than the other chromosomes, or they lacked a mate for synapsis, or they were distributed to only half of the sperm. The vast majority of the observations were made on males since, for technical reasons, spermatogenesis was easier to study than oogenesis.

MCCLUNG 1901:
THE X DETERMINES MALENESS

In 1901 the American cytologist, C. E. McClung, suggested that the **X** chromosome was in some way connected with the determination of sex.

> Being convinced from the behavior in the spermatogonia and the first spermatocytes of the primary importance of the accessory chromosome, and attracted

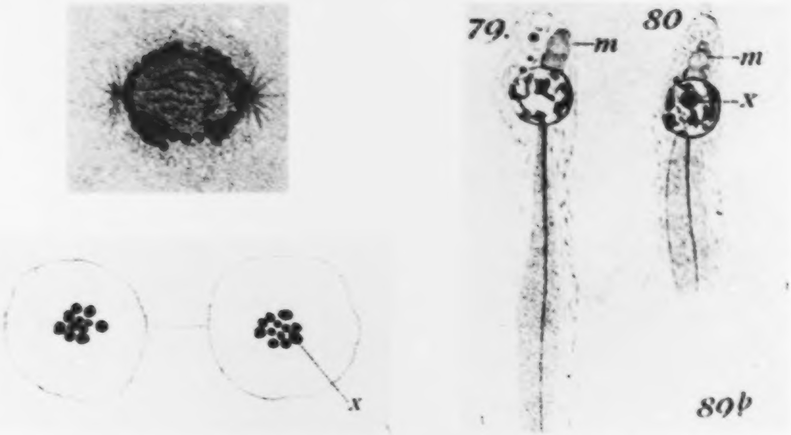


FIG. 21. Meiosis in *Pyrrhocoris.* The upper left figure is of a spermatocyte in telophase of the second meiotic division. The **X** chromosome, lagging behind the rest, is going to the pole at the right. The resulting daughter cells are shown at the lower left figure with the **X** in the right cell only. Two sorts of sperm will be formed, as shown in the rightmost figure—one with an **X** and one without. (Henking, 1891)

> by the unusual method of its participation in the spermatocyte mitoses [*i.e.*, meiosis], I sought an explanation that would be commensurate with the importance of these facts. Upon the assumption that there is a qualitative difference between the various chromosomes of the nucleus, it would necessarily follow that there are formed two kinds of spermatozoa which, by fertilization of the egg, would produce individuals qualitatively different. Since the number of each of these varieties of spermatozoa is the same, it would happen that there would be an approximately equal number of these two kinds of offspring. We know that the only quality which separates the members of a species into these two groups is that of sex. I therefore came to the conclusion that the accessory chromosome is the element which determines that the germ cells of the embryo shall continue their development past the slightly modified egg cell into the highly specialized spermatozoon.
>
> It would not be desirable in a preliminary paper of this character to extend it by a detail of the discussion by which the problem was considered. Suffice it to say that by this assumption it is possible to reconcile the results of many empirical theories which have proved measurably true upon the general ground that the egg is placed in a delicate adjustment with its environment, and in response to this, is able to attract that form of spermatozoon which will produce an individual of the sex most desirable to the welfare of the species. The power of selection which pertains to the female organism is thus logically carried to the female element.
>
> Numerous objections to this theory received consideration, but the proof in support of it seemed to overbalance them largely, and I was finally induced to commit myself to its support. I trust that the element here discussed will attract the attention which I am convinced it deserves and can only hope that my investigations will aid in bringing it to the notice of a larger circle of investigators than that now acquainted with it.

This hypothesis *was* noticed since it provided an explanation for those odd chromosomes that were being found in more and more species. Montgomery (1901) had observed several cases. Sutton (1902) had described the same condition for *Brachystola* and wrote,

> thus we seem to find a confirmation of McClung's suggestion that the accessory chromosome is in some way concerned with the determination of sex. (p. 36)

At first it was believed that the accessory chromosomes were extra and restricted to males. Sutton had reported that the chromosomes of ovarian cells resembled those in the testis except for the lack of the accessory. Subsequently it was discovered that the female of *Brachystola*, far from lacking the accessory chromosome, has two.

Thus McClung had proposed a fruitful hypothesis—if we exclude that extraordinary suggestion in paragraph two of the quotation that the ovum can choose which type of sperm will enter, and do it for the welfare of the species.

Wilson 1905–1912: Sex Chromosomes

By the time McClung proposed that the accessory or **X** chromosomes were somehow involved in sex determination, they had been observed in a variety of species. Since this was a most important hypothesis, many species of both animals and plants were studied to see to what extent the hypothesis was supported.

During the first decade of the 20th century the study of sex chromosomes exhibited a pattern not uncommon in science. An important hypothesis, presumably of wide applicability, is proposed—although on inadequate evidence. This was McClung's (1901) suggestion that the accessory chromosome might determine maleness. This initial suggestion was followed by a period of active research. There emerged conflicting observations and it was clear that the original suggestion that males have an extra chromosome did not hold for all species. There were also conflicting conclusions. Some investigators failed to find accessory chromosomes. Those who did suggested a variety of hypotheses to account for them. Some believed them to be degenerating chromosomes, others believed them to be a special type of nucleolus, and still others thought that McClung was probably correct.

The final stage in this scenario is when one or a few individuals, careful of their supporting data and cautious in their conclusions, bring conceptual order to the subject being investigated. And, again, as so often happens, two or more individuals, working independently, reach essentially the same conclusion at the same time. E. B. Wilson was the person mainly responsible for solving the riddle of the accessory chromosomes but the announcement of his discovery coincided with a report reaching similar conclusions by Nellie M. Stevens.

Wilson (1905*c*) begins as follows:

> Material procured during the past summer demonstrates with great clearness that the sexes of Hemiptera show constant and characteristic differences in the chromosome groups, which are of such a nature as to leave no doubt that a definite connection of some kind between the chromosomes and the determination of sex exists in these animals. These differences are of two types. In one of these, the cells of the female possess one more chromosome than those of the male; in the other, both sexes possess the same number of chromosomes, but one of the chromosomes in the male is much smaller than the corresponding one in the female (which is in agreement with the observations of Stevens on the beetle *Tenebrio*). These types may conveniently be designated as A and B respectively. [Subsequently A was to be called **XX** female–**XO** male and B was to become **XX** female–**XY** male.] . . . .
>
> These facts admit, I believe, of but one interpretation. Since all of the chromosomes in the female (oogonia) may be symmetrically paired, there can be no doubt that synapsis in this sex gives rise to the reduced number of symmetrical bivalents, and that consequently all of the eggs receive the same number of chromosomes. This number . . . is the same as that present in those spermatozoa that contain the 'accessory' chromosomes. It is evident that both forms of spermatozoa are functional, and that in type A females are produced from eggs fertilized by spermatozoa that contain the 'accessory' chromosome, while males are produced from eggs fertilized by sper-

> matozoa that lack this chromosome (the reverse of the conjecture made by McClung).

The situation in type B species was essentially the same, except that one class of sperm contained the **X** and the other the **Y**.

Stevens (1905) summarized her discovery as follows:

> From the standpoint of sex determination, we have in *Tenebrio molitor* the most interesting of the forms considered in this paper. In both somatic and germ cells of the two sexes there is a difference not in the number of chromatin elements, but in the size of one, which is very small in the male and of the same size as the other 19 in the female. The egg nuclei of the female must be alike so far as number and size of the chromosomes are concerned, while it is absolutely certain that the spermatids are of two equal classes as to chromatin content of the nucleus—one half of them have the 9 large chromosomes and 1 small one, while the other half have 10 large ones. Since the male somatic cells have 19 large and 1 small chromosome, while the female somatic cells have 20 large ones, it seems certain that an egg fertilized by a spermatozoon which contains the small chromosome must produce a male, while the one fertilized by a spermatozoon containing 10 chromosomes of equal size must produce a female. (p. 18)

Neither Wilson's nor Stevens' reports mention the great difficulty in studying chromosomes. In *Tenebrio,* for example, all the autosomes are identical in appearance—and very small. The male differs by having that one small chromosome—and many observers might have missed it. Figure 22, from Stevens' paper, shows the type of illustration that was usual in cytological reports of the time. Tissue sections would be searched for cells that showed the full set of chromosomes. Her 207 shows an ovarian follicle cell with the 20 large chromosomes. In 208a and 208b, part of the chromosomes were in one section and the rest in the adjacent section. The diploid set of chromosomes of the male is shown in 169 and 170. Number 196 shows the monoploid number in spermatids with the 9 large and the 1 small chromosome and 197 shows those with the 10 large chromosomes.

Considering the difficulty in working with such material, it is not surprising that most problems in cytology had a shaky beginning.

Wilson's most important contributions are contained in eight long papers, *Studies on Chromosomes I—VIII,* published between 1905 and 1912. His own observations, together with those of others, revealed a complexity not imagined by McClung and Sutton. In most groups of animals the female has a pair of homologous **X** chromosomes and is designated as **XX**. The males of various species, on the other hand, vary considerably. Some have only a single **X** and are designated as **XO**—the "**O**" indicating the absence of a chromosome (Fig. 23).

In other species the males may have two chromosomes, one like the **X** of the female and the other, usually differing in size or shape, called the **Y**. Thus these males are designated **XY**. With respect to the sex chromosomes, the males in this case produce two sorts of sperm, **X**-carrying sperm and **Y**-carrying sperm and thus are heterogametic. The females produce a single type of ovum and hence are homogametic. [It was found later that both human beings and *Drosophila* are of the **XX** female and **XY** male type.]

These two patterns of sex chromosomes, while the ones most commonly encountered, do not exhaust the range of possibilities. Some species may have multiple sex chromosomes. In birds and Lepidoptera the females are heterogametic and the males homogametic for the sex chromosomes.

These are some of the conclusions that can be drawn from the numerous studies of Wilson, Stevens, and others.

1. The sex of an offspring is determined at the time of fertilization.
2. The sex of an individual will be irreversible if it is based solely on the sex chromosomes—unless we can alter the chromosomes.
3. If meiosis is normal and fertilization

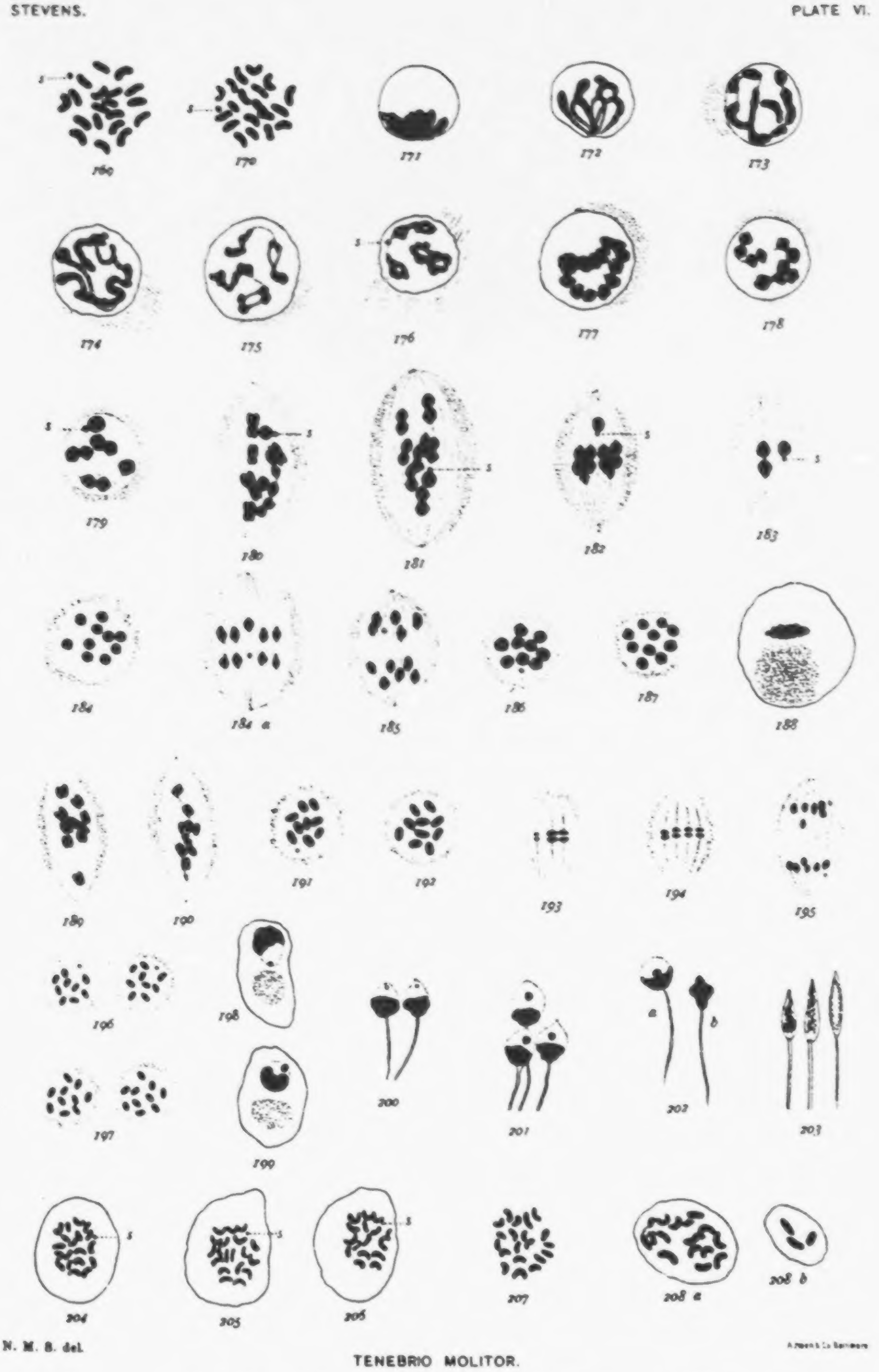


FIG. 22. The chromosomes of *Tenebrio.* (N. Stevens, 1905)

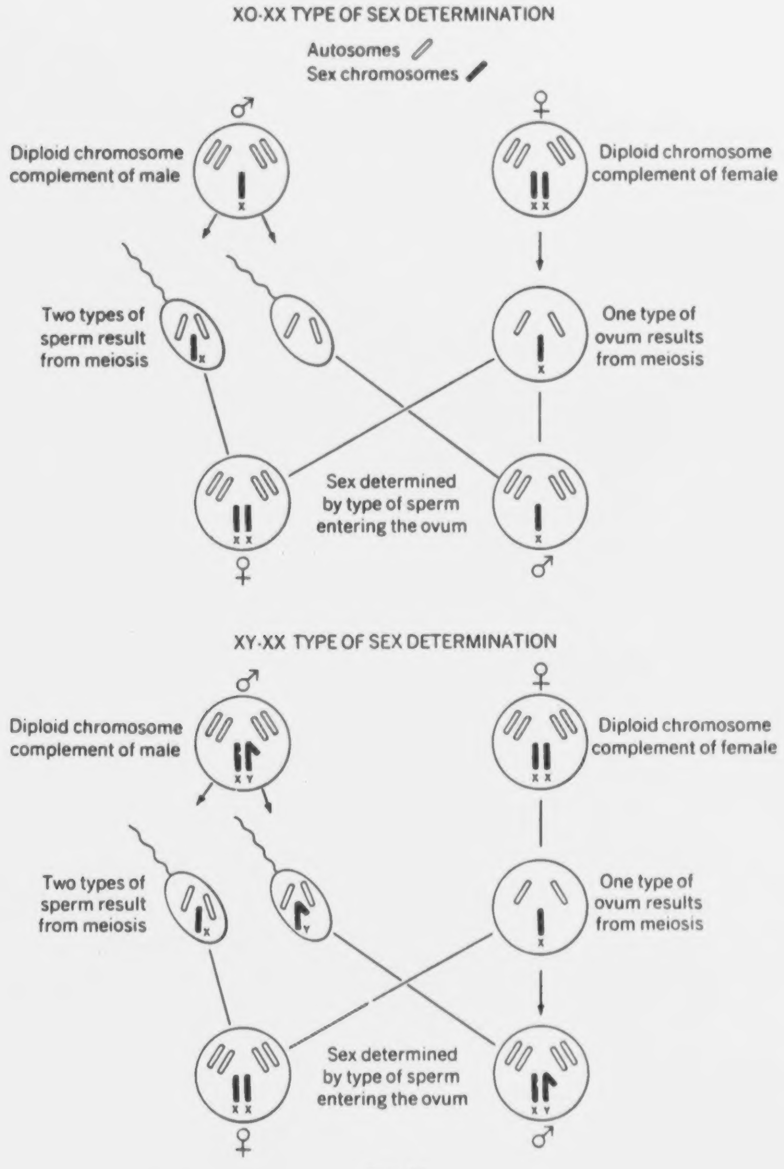

XO-XX TYPE OF SEX DETERMINATION
Autosomes
Sex chromosomes
♂
♀
Diploid chromosome complement of male
Diploid chromosome complement of female
X
X X
Two types of sperm result from meiosis
One type of ovum results from meiosis
Sex determined by type of sperm entering the ovum
♀
♂
XY-XX TYPE OF SEX DETERMINATION
♂
♀
Diploid chromosome complement of male
Diploid chromosome complement of female
X Y
X X
Two types of sperm result from meiosis
One type of ovum results from meiosis
Sex determined by type of sperm entering the ovum
♀
♂

FIG. 23.

is random, the two sexes should be produced in approximately equal numbers.

4. The relation between sex and chromosomes, firmly established by 1910, is additional evidence supporting Sutton's hypothesis that chromosomes are the basis of inheritance.

1910: POSSIBLE CONCLUSIONS ABOUT THE PHYSICAL BASIS OF INHERITANCE

On 13 December 1910, Wilson finished writing *Studies on Chromosomes VII* (1911). A few months earlier his colleague, Thomas Hunt Morgan, had published a brief note on *Sex Limited Inheritance in Drosophila*

(1910*a*). Morgan's paper described the first of the experiments that were to be taken by almost all biologists as the "final proof" that genes are parts of chromosomes. After our survey of the work of Montgomery, Sutton, Boveri, McClung, and Wilson one might have suspected that no "final proof" was needed—the case was already convincing. But that was not so. Wilson, always cautious, wrote:

> Studies on the chromosomes have steadily accumulated evidence that in the distribution of these bodies we see a mechanism that *may* be competent to explain some of the most complicated of the phenomena that are brought to light by the study of heredity. New and direct evidence that the chromosomes are in fact concerned with determination has been produced by recent experimental studies, notably by those of Herbst ('09) and Baltzer ('10) on hybrid sea-urchin eggs. But the interest of the chromosomes for the study of heredity is not lessened, as some writers have seemed to imply, if we take the view—it is in one sense almost self-evident—that they are not the exclusive factors of determination. Through their study we may gain an insight into the operation of heredity that is none the less real if the chromosomes be no more than one necessary link in a complicated chain of factors. From any point of view it is indeed remarkable that so complex a series of phenomena as is displayed, for example, in sex-limited heredity [*i.e.*, Morgan's just-published research] can be shown to run parallel to the distribution of definite structural elements, whose combinations and recombinations can in some measure actually be followed with the microscope. Until a better explanation of this parallelism is forthcoming we may be allowed to hold fast to the hypothesis, directly supported by so many other data, that it is due to a direct causal relation between these structural elements and the process of development. (p. 106)

"This parallelism" allows deductions to be made, as noted before. Here is one related to sex chromosomes: *If genes are parts of the sex chromosomes, one must expect the inheritance of these genes to follow the inheritance of the sex chromosomes.*

Consider for example the case of a gene of the **X** chromosome of a species with **XX** females and **XY** males (Fig. 23). The distribution of these chromosomes is such that a male offspring can receive his **X** only from his mother (if he also received an **X** from his father, he would be a daughter). Daughters on the other hand receive an **X** from each parent. In a similar manner, any genes of the **Y** chromosome are transmitted exclusively through males.

Following a list of references, we shall begin the test of that deduction.

REFERENCES TO MENDELISM AND CYTOLOGY, 1900–1910

The decade between the rediscovery of Mendel's paper and the beginning of the work of the Morgan school with *Drosophila* saw great activity. There are two essentially independent lines of research, namely breeding and cytology—with a few tentative attempts to unite them. The literature is enormous and the following serves only as an introduction.

General works. Bateson (1894, 1900*a*, 1900*b*, 1902, 1906, 1908, *1909, 1913*b*, 1914, 1916, 1920, 1926, 1928), Bateson *et al.* (1902, 1905, 1906, 1908, 1911), Boveri (1902, 1907), Cannon (1902, 1903*a*, 1903*b*), Castle (1903, 1911), Chubb (1910–1911), Conklin (1908), O. F. Cook (1907), Correns (1900), Crew (1965, 1966), Darbishire (1911), Davenport (1901, 1907), Galton (1889, 1897), Henking (1891), Hurst (1925), Johannsen (1911), Lock (*1906), McClung (1901), Mendel (1865, 1902), Mitchell (1910–1911), Montgomery (1901), Moore (1972*a*,), Morgan (1903, 1909, 1913), Pearson (1898), Punnett (1911), Schrader (1928), Sharp (1934), Spillman (1902), Sutton (1902, 1903), Tschermak (1900), Vernon (1903), de Vries (1900, 1901–1903, 1906, 1909–1910, 1919), Weldon (1902), Wheldale *et al.* (1909), E. B. Wilson (1902, 1903, 1905*a*, 1905*b*, 1905*c*, 1906, 1909*a*, 1909*b*, 1909*c*, 1910, 1911, 1912, *1914, 1924, *1925), Wright (1966).

History, biography, and anthologies. G. E.

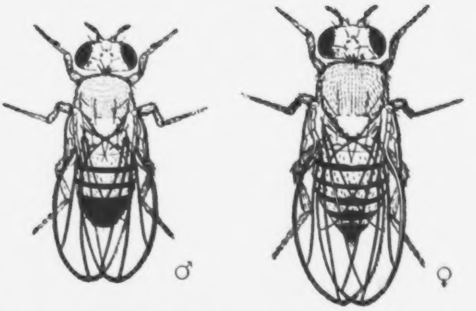


FIG. 24. Male (left) and female (right) of *Drosophila melanogaster*. (Morgan, 1919)

Allen (1966*a*, 1966*b*, 1969, 1974*a*, 1974*b*, 1976, 1978, 1979, 1985), Babcock (1949–1951), Baltzer (1964, 1967), B. Bateson (1928), Bennett (1965), Boyes (1966), Brink (1967), Carlson (1967*a*, 1967*b*), Castle (1951), Coleman (1965, 1970*a*, 1970*b*, 1971), Conklin (1913), Crampton (1942), Crew (1968), Darlington (1960, 1969), Dodson (1955), Dorsey (1944), Dunn (*1951, *1965*a*, 1965*b*, 1969), East (1922, 1923), Eichling (1942), Fantini (1985), Fisher (1936), Fong (1969), Gabriel and Fogel (1955), Gasking (1959), Genetics (1950), Glass (1947, 1953, 1959*a*), Hughes (1959), Iltis (1932, 1947, 1951), Kalmus (1983), Krizenecky (1965), McKusick (1960, 1976), Mayr (1973, *1982), Moore (1972*a*, 1972*b*, 1983), Morgan (1926*b*, 1940), Muller (1943), Nardone (1968), Olby (*1966, 1979), Oppenheimer (1970), Orel (1968, 1984), Orel and Varva (1968), Pearson (1924), Peters (1959), Pollister (1974), Provine (*1971), Punnett (1950), Robinson (1979), Root-Bernstein (1983), Rosenberg (1976), Stern and Sherwood (*1966), Stomps (1954), Stubbe (*1972), Sturtevant (*1965*a*, 1965*b*), Sutton (1917), Tschermak (1951), Voeller (1968), Weir (1968), Wilkie (1962), Winge (1958), Zirkle (1951*a*, 1964, 1968*a*, 1968*b*).

A FLY WITH WHITE EYES

The most famous fly in the history of science is a male fruit fly with the name *Drosophila melanogaster* (Fig. 24). This individual became famous because it had white eyes instead of the normal red ones, but most importantly because it happened to appear in Room 613 of Schermerhorn Hall at Columbia University in the spring of 1910. This was the "Fly Room," the laboratory of Thomas Hunt Morgan and a remarkable group of young students. Down the hall was the laboratory of E. B. Wilson, who was finishing up his series—*Studies on Chromosomes.*

That fly had chosen the proper time and place to spin out its short life and achieve immortality.

Morgan (1910*a*) tells the story:

> In a pedigree culture of *Drosophila* which had been running for nearly a year through a considerable number of generations a male appeared with white eyes. The normal flies have brilliant red eyes.
>
> The white-eyed male, bred to his red-eyed sisters, produced 1,237 red-eyed offspring, (F_1), and 3 white-eyed males. The occurrence of these three white-eyed males (F_1) (due evidently to further sporting) will, in the present communication, be ignored.
>
> The F_1 hybrids, inbred, produced:
>
> 2,459 red-eyed females,
> 1,011 red-eyed males,
> 798 white-eyed males.

(If time permits, this might pose an interesting problem for the class to consider—overnight, perhaps.)

> *No white-eyed females appeared.* The new character showed itself therefore to be sex limited in the sense that it was transmitted only to the grandsons. But that the character is not incompatible with femaleness is shown by the following experiment.
>
> The white-eyed male (mutant) was later crossed with some of his daughters (F_1), and produced:
>
> 129 red-eyed females,
> 132 red-eyed males,
> 88 white-eyed females,
> 86 white-eyed males.
>
> The results show that the new character, white-eyes, can be carried over to the females by a suitable cross, and is in consequence in this sense not limited to one

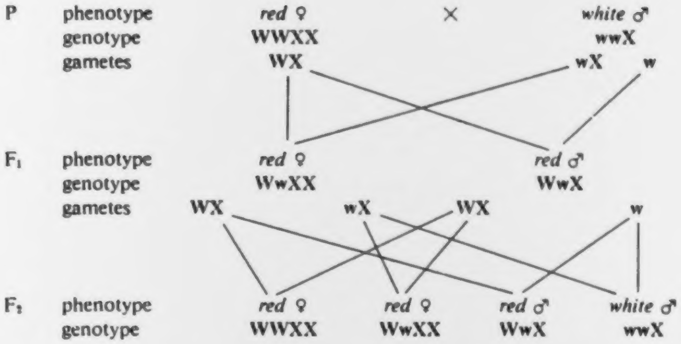


FIG. 25. Morgan's first hypothesis to explain the inheritance of *white eyes.*

> sex. It will be noted that the four classes of individuals occur *roughly* in equal numbers (25 per cent.).

What was one to conclude? The original cross of the *white-eyed* male with the *red-eyed* females gave an F_2 ratio of 4.3 to 1. This might be accepted as a 3 to 1 ratio since it seemed clear that the *white-eyed* flies were less viable than their *red-eyed* sibs (as shown in the later cross of the F_1 daughters with the *white-eyed* male).

But to interpret this as a typical 3 to 1 F_2 ratio was spurious. White eye color was not evenly distributed among females and males as it should be in a normal Mendelian cross. In the F_2 of the original cross there were no *white-eyed* females. This association of inheritance with sex hinted that a critical test of Sutton's hypothesis might be in the making. Back to Morgan:

MORGAN'S FIRST HYPOTHESIS

> *An Hypothesis to Account for the Results.*—The results just described can be accounted for by the following hypothesis. Assume that all of the spermatozoa of the white-eyed male carry the "factor" for white eyes "W"; that half of the spermatozoa carry a sex factor "X" the other half lack it, *i.e.*, the male is heterozygous for sex. Thus the symbol for the male is "WWX," and for his two kinds of spermatozoa WX—W.
>
> Assume that all of the eggs of the red-eyed female carry the red-eyed "factor" R; and that all of the eggs (after reduction) carry one X, each, the symbol for the red-eyed female will be therefore RRXX and that for her eggs will be RX—RX.

It is of the greatest interest to note how Morgan indicated the genotype of both adults and gametes. He recognized both genetic "factors" *and* chromosomes as though they were independent phenomena. His symbolism of "R" for the allele for red-eyes and "W" for the allele for white was eventually replaced by the Mendelian scheme for using upper and lower case symbols for dominant and recessive alleles so, for clarity, I will alter Morgan's original notation and use **w** for the allele for *white eyes* and **W** for the allele for *red eyes.* Another point to be noted is that the male was assumed to have only one **X** chromosome, that is, to be of an **XO** type of male. Subsequently it was realized that the *Drosophila* male has a **Y** chromosome as well.

Figure 25 uses Morgan's hypothesis to explain the results of the first cross of the *white-eyed* male with a red-eyed female. The scheme fits the data, that is, the F_1 is predicted to consist only of *red-eyed* daughters and *red-eyed* sons. Continuing to the F_2, the hypothesis predicts that all of the females will have *red eyes* and that half of the sons will have *red eyes* and half will have *white eyes.*

Not surprisingly the hypothesis predicts what was found. After all, the observations were made before the hypothesis was formulated and there would be no reason to propose a hypothesis that failed to account for the data already at hand.

But the hypothesis explained the data only with one important qualification. Note the F_1 individuals. When gametes are formed by the female, half are shown with the **W** going with an **X** and half with the **w** going with an **X**. However, the hypothesis demanded a very different situation for the F_1 male. The male is shown as **WwX**. One should expect, therefore, four classes of gametes: **WX**, **wX**, **W** (or **WO**), and **w** (or **wO**). Morgan recognized only two classes of sperm: **WX** and **w**. He explains:

> It is necessary to assume . . . that when the two classes of spermatozoa are formed in the F_1 red male (WwX), W and X go together—otherwise the results will not follow (with the symbolism here used). This all-important point can not be fully discussed in this communication.

TESTING THE FIRST HYPOTHESIS

The value of a hypothesis is not only to explain the data at hand but also to predict what will happen in new situations. Morgan undertook four tests of his hypothesis.

1. If the genotype of the *white* males is **wwX** and of the *white* females **wwXX**, their offspring should consist of *white* males and *white* females only. The diagrammatic representation of this cross in terms of Morgan's hypothesis is shown in Figure 26. The cross was made and the results were according to predictions.

2. The F_2 *red-eyed* females in the first cross (Fig. 25), were predicted to be of two genotypes, **WWXX** and **WwXX**, even though all were identical in appearance. If several of these females were crossed individually with *white-eyed* males, one would expect two results as shown in Figure 26. Approximately half of the crosses should result in all of the offspring having *red* eyes and the other half should produce four phenotypes among the offspring. These crosses were made and the predicted results were observed.

3. The genotype of the F_1 female of the original cross (Fig. 25) was predicted to be **WwXX**. If so, the cross of such a female with a *white-eyed* male should give the same results as shown in Test 2b of Figure 26. Again the cross was made and the predicted outcome was observed.

4. The hypothesis requires that the original F_1 males (Fig. 25) be **WwX**. If such a male is crossed with a *white-eyed* female, the prediction would be for *red-eyed* females and *white-eyed* males, as shown in Figure 26. The crosses were made and the prediction verified. Once again, however, the hypothesis required an unusual type of meiosis in the **WwX** males: the **W** factor would always be with the **X**, to form **WX** sperm; there could be no **wX** sperm.

TRUE, BEYOND ALL REASONABLE DOUBT?

Well, maybe. Few new hypotheses in the early days of genetics, apart from Mendel's, were tested so thoroughly as this one. Nearly all of Morgan's first hypothesis was based on well-substantiated genetic principles: dominance and recessiveness, segregation, and the behavior of sex chromosomes. His four deductions were explicit and critical. In every case the experiments to test the deductions provided data that verified the predictions.

To be sure there was that qualification about spermatogenesis in **WwX** males but by 1910 his colleague Wilson, and other cytologists, were reporting all sorts of strange behavior of chromosomes in meiosis. There was no *a priori* reason to exclude the hypothesis of the association of **W**, but never **w**, with the **X** in males.

Morgan reported another discovery that was difficult to explain:

> A most surprising fact appeared when a white-eyed female was paired to a wild, red-eyed male, *i.e.*, to an individual of an unrelated stock. The anticipation was that wild males and females alike carry the factor for red eyes, but the experiments showed that all wild males are heterozygous for red eyes, and that all the wild females are homozygous. Thus when the white-eyed female is crossed with a wild red-eyed male, all of the female offspring are red-eyed, and all of the male offspring white-eyed.

These data presented a difficulty. If all males in natural populations are hetero-

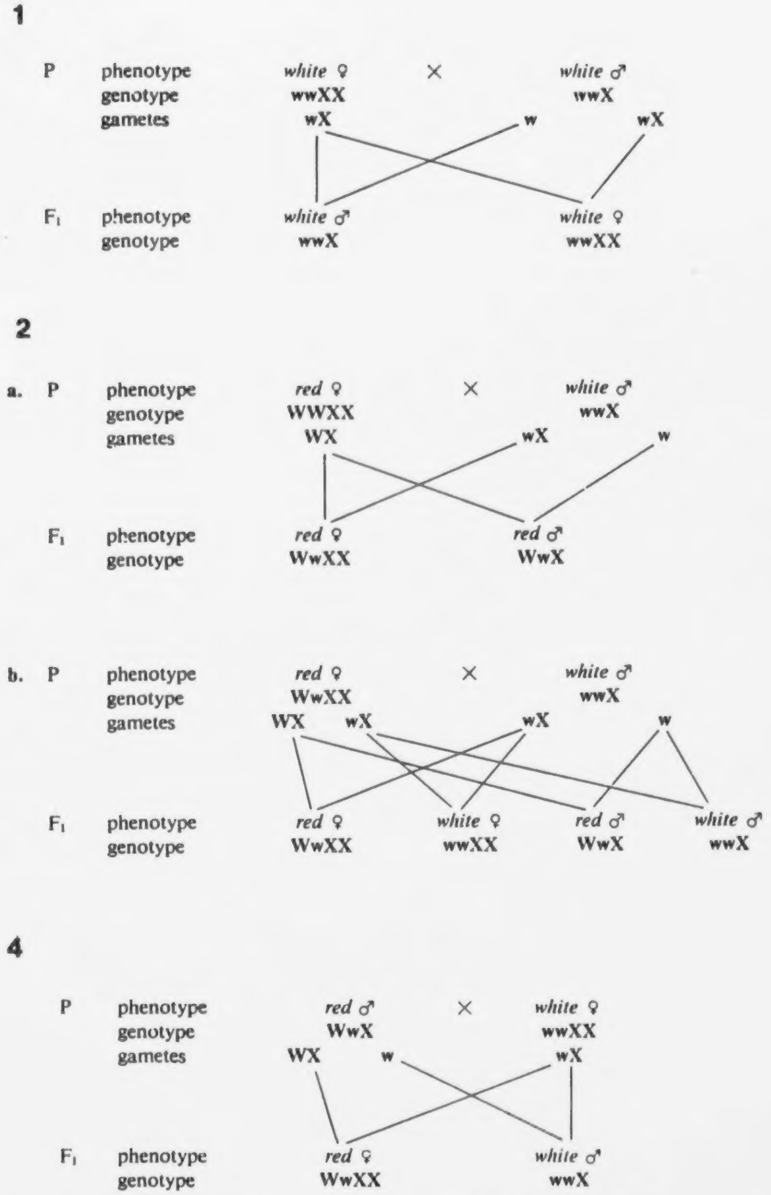

1
P phenotype white ♀ × white ♂
genotype wwXX wwX
gametes wX w wX
F₁ phenotype white ♂ white ♀
genotype wwX wwXX
2
a. P phenotype red ♀ × white ♂
genotype WWXX wwX
gametes WX wX w
F₁ phenotype red ♀ red ♂
genotype WwXX WwX
b. P phenotype red ♀ × white ♂
genotype WwXX wwX
gametes WX wX wX w
F₁ phenotype red ♀ white ♀ red ♂ white ♂
genotype WwXX wwXX WwX wwX
4
P phenotype red ♂ × white ♀
genotype WwX wwXX
gametes WX w wX
F₁ phenotype red ♀ white ♂
genotype WwXX wwX

FIG. 26. Tests of Morgan's first hypothesis to explain the inheritance of *white eyes.*

zygous for these eye color alleles, one would expect numerous *white-eyed* flies to be present in wild populations and in cultures. Yet Morgan had been raising *Drosophila* for many months and had observed no such thing.

As yet I have found no evidence that white-eyed sports occur in such numbers. Selective fertilization may be involved in the answer to this question.

There are many interesting points about this famous paper that started the line of experimentation that revolutionized genetics. The most puzzling is why Morgan failed to realize that the data could be explained more simply by assuming that the alleles for eye color were *parts* of the **X** chromosome. Instead he treated the situation almost as a dihybrid cross. To be sure in 1910 he was still most suspicious of the Suttonian hypothesis but would he not have discussed the data with his colleague Wilson? To be sure the paper had been written in haste. G. E. Allen (1978, p. 153) estimates that the *white-eyed* male was discovered about January of 1910. Then the experiments were done. The paper was finished 7 July 1910 after Morgan had gone to Woods Hole, and was published in the 22 July 1910 issue of *Science.*

Of considerable pedagogical interest is the fact that the paper is written in a form that corresponds to the popular view of "The Scientific Method." First there are the observations of some natural phenomenon, in this case the crosses involving the strange new fly with the white eyes. Then a hypothesis is formulated. Finally deductions are made from the hypothesis and these are tested. The tests are assumed to have supported the hypothesis so the scientist goes on to the next problems. These steps are rarely mentioned in published reports, even though something like the "scientific method" is happening in the mind of the investigator. Morgan's 1910*a* paper is unusual in that these steps are explicitly stated in the published report.

MORGAN'S SECOND HYPOTHESIS

It took Morgan only a few months to realize that his first hypothesis to explain sex-limited inheritance of eye color was fundamentally flawed. Several additional mutations were found and these were inherited in the same manner as the *white-eyed* allele. The results were "first announced in a public lecture given in the Marine Biological Laboratory at Woods Hole, Mass., July 7, 1911" (Morgan, 1911*a*, p. 365). The new hypothesis was simplicity itself: instead of thinking of the sex-limited alleles as being associated with the **X** chromosomes (the first hypothesis) why not think of them as part of the **X** chromosome?

> The experiments on Drosophila have led me to two principal conclusions:
>
> First, *that sex-limited inheritance is explicable on the assumption that one of the material factors of a sex-limited character is carried by the same chromosomes that carry the material factor for femaleness.*
>
> Second, *that the 'association' of certain characters in inheritance is due to the proximity in the chromosomes of the chemical substances (factors) that are essential for the production of those characters.* (Morgan, 1911*a*, p. 365)

Therefore, if one assumes that the allele for *white eyes* and the dominant allele for *red eyes* are parts of the **X** chromosome, the results of all the crosses correspond to what would be expected from the distribution of the **X** chromosome in meiosis and fertilization. It would then be unnecessary to invoke subsidiary assumptions, such as the **w** allele not being able to associate with the **X** in meiosis of the **WwX** males or that all wild males must be heterozygous.

Morgan's second hypothesis has withstood every conceivable test and it can be accepted as true beyond all reasonable doubt. Figure 27 shows how it explains the inheritance of *white eyes.* This figure also shows a **Y** chromosome because it was soon realized that the male *Drosophila* is **XY**, not **XO**. The data indicated that the **Y** chromosome did not have an allele at the locus for *white eyes* and, as we now know, it has only a very few active gene loci of any sort.

THE NON-OBVIOUSNESS OF THE "OBVIOUS"

Once again we find an example of the "obvious" not being obvious at all. More often than not, things become obvious after the fact. One is reminded of the oft-quoted remark of Thomas Henry Huxley when the concept of natural selection became clear to him:

> My reflection, when I first made myself

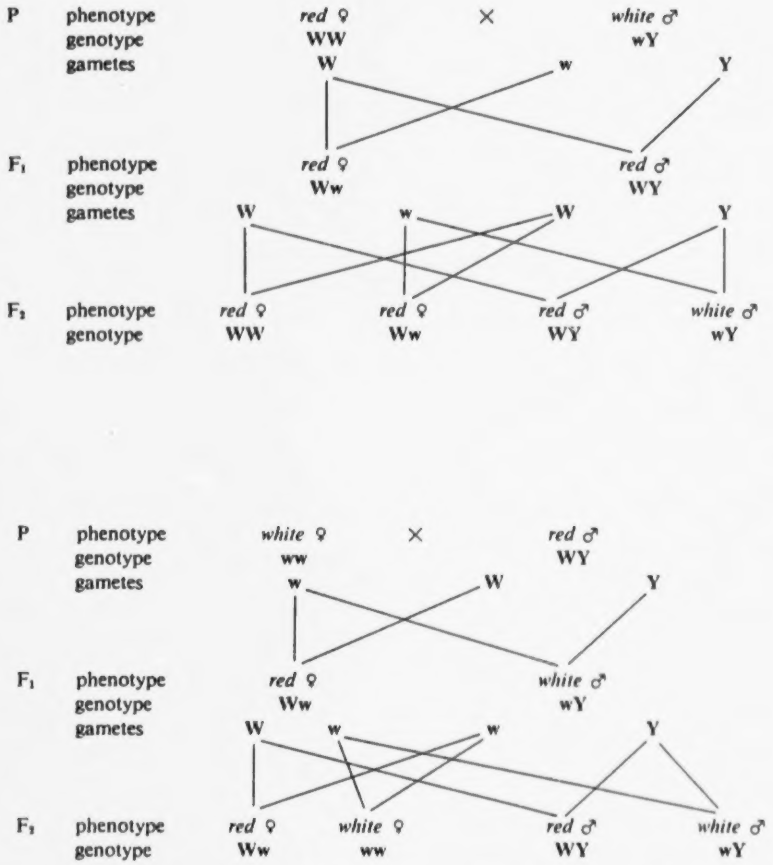


FIG. 27. Morgan's second hypothesis to explain the inheritance of *white eyes*.

> master of the central idea of the 'Origin' was, 'How extremely stupid not to have thought of that'. (Huxley, 1868, p. 197)

Morgan was in the Zoology Department where a short seven years earlier Sutton had maintained that genes must be parts of chromosomes. His colleague E. B. Wilson had continued to work within the Suttonian paradigm. However, Morgan had not accepted the chromosomes as the physical basis of inheritance and was not to do so until his own experiments convinced him. In fact, he had a poor opinion of the explanations being used by geneticists to account for the data of inheritance. In January 1909, the year before his first paper on the *white-eyed* fly, he had this to say in a lecture to the American Breeders' Association:

> In the modern interpretation of Mendelism, facts are being transformed into factors at a rapid rate. If one factor will not explain the facts, then two are invoked; if two prove insufficient, three will sometimes work out. The superior jugglery sometimes necessary to account for the results may blind us, if taken too naively, to the common-place that the results are often so excellently "explained" because the explanation was invented to explain them. We work backwards from the facts to the factors,

> and then, presto! explain the facts by the very factors that we invented to account for them . . . . I cannot but fear that we are rapidly developing a sort of Mendelian ritual by which to explain the extraordinary facts of alternative inheritance. (p. 365)

Such was the opinion of the one who, in a few short years, was to be recognized as the Giant of Genetics of our century—and who surely will be the last giant of genetics working above the molecular level.

Morgan, together with many others, was still troubled in 1909 by the notion of the "purity of the gametes." He continues in his lecture to the American Breeders' Association:

> I should like to point out certain implications in the current assumption that the factors (sometimes referred to as the actual characters themselves—unit-characters, not infrequently) are dissociated in the germ-cells of the hybrids into their allelomorphs. For instance a tall pea crossed with a dwarf pea produces in the first generation a tall hybrid. Such tall peas inbred produce three tall peas to one dwarf. Such are the surprising facts. Mendel pointed out that the numerical results could be explained if we assume that the hybrid peas produce germ-cells of two kinds, tall-producing and dwarf-producing. The simplicity of the explanation, its wide applicability and what I may call its intrinsic probability will recommend his interpretation to all who have worked with such problems of heredity. Out of this assumption the modern factor hypothesis has emerged. The tallness of the tall pea is said to be due to a tall-factor; the dwarfness of the dwarf-pea, to be a dwarfness factor. When they meet in the hybrid, the tall-factor gets the upper hand. So far we do little more than restate Mendel's view. But when we turn to the germ-cells of the hybrid we go a step further. We assume that the tall-factor and the dwarf-factor retire into separate cells after having lived together through countless generations of cells without having produced any influence on each other. We have come to look upon them as entities that show a curious antagonism, so that when the occasion presents itself, they turn their backs on each other and go their several ways. Here it seems to me is the point where we are in danger of over-looking other possibilities that may equally well give us the two kinds of germ-cells that the Mendelian explanation calls for. (pp. 365–366)

Morgan then proposed a vague alternative mechanism that reveals his basic training as an embryologist. He detects an element of preformation (a red flag to the embryologists) in the hypotheses of the geneticists. His proposed hypothesis involved "alternative states of stability," "local conditions," "changes in equilibrium," and interactions between homologous chromosomes. This seems out of character for Morgan—always one to insist on experimentation as the proper way to understanding. He was rejecting a hypothesis that was far more amenable to experimental verification in favor of one serviceble only for speculation.

But Morgan did not have an entirely closed mind. After rejecting the hypothesis, well into 1909, that the segregation of alleles in Mendelian crosses could be explained by the segregation of chromosomes in meiosis, he became the strongest proponent of the hypothesis that Mendelism finds its explanation in the behavior of chromosomes.

THE "FLY ROOM"

In the decade of the 1910s a medium-sized room in the Zoology Department of Columbia University, occupied by Morgan and his students, became the center of genetics. In 1911 Morgan (1866–1945) was 45 years old. He had come to Columbia in 1904 as a world-class embryologist. Throughout this formative decade he had three close associates, who began as his students and remained as co-workers: Sturtevant, Bridges, and Muller. Alfred Henry Sturtevant (1891–1970) was to receive his Ph.D. in 1914 for using linkage data to construct the first genetic map of chromosomes. Calvin B. Bridges (1889–1938) received his Ph.D. in 1916 for a classic

FIG. 28. Edmund Beecher Wilson.

paper on non-disjunction, widely regarded as the final and conclusive proof that genes are parts of chromosomes. Herman J. Muller (1890–1967) received his degree in 1915 for a definitive study of crossing-over. Biologists came from all over the world to visit or to do research in the Fly Room. The room and some of those associated with it are shown in Figures 28–31.

The basis for all these discoveries was the fruit fly, *Drosophila melanogaster.* It appears to be an immigrant from the Old World and as a "domestic species" is frequently found in homes, stores, and garbage dumps—wherever there is fresh fruit. It has also spread into more natural habitats and in some areas is the most abundant species of its genus.

Morgan began to use *Drosophila* because he was unable to obtain funds for experiments on mammals. *Drosophila* could be raised in large numbers on inexpensive food, at first bananas, in small milk bottles, which Morgan apparently appropriated from those brought to his home by the local milkman. A few other laboratories were using *Drosophila* at the same time (G. E. Allen, 1975*a*) and there has been much speculation about where Morgan obtained the stocks of those famous flies. There is no reason to believe that there was a single source. When I was a student at Columbia

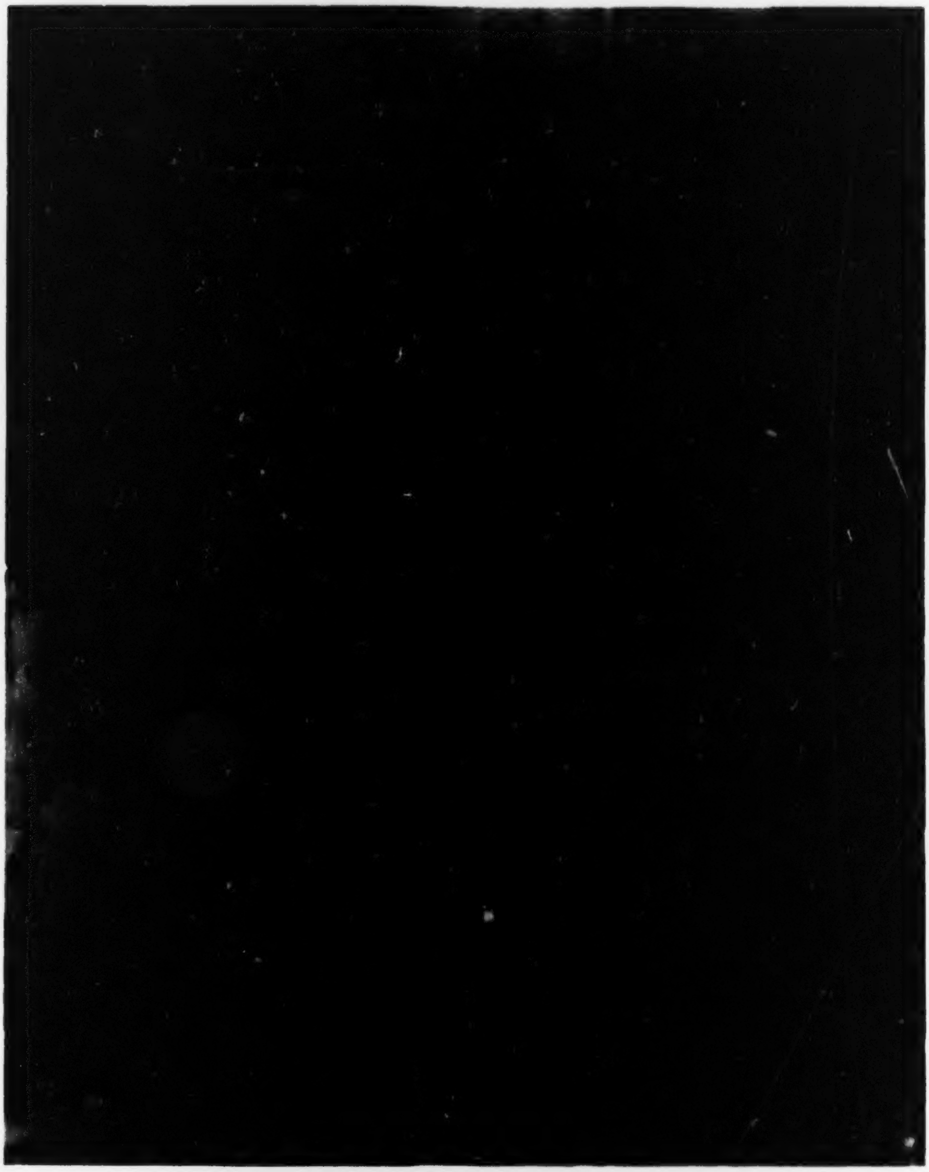


FIG. 29. Thomas Hunt Morgan in the Fly Room. Taken about 1917 by Calvin Bridges.

in the 1930s, the source was remembered as a pineapple on the window sill outside of Morgan's laboratory. The discovery of the *white-eyed* male was credited to Calvin Bridges. He was at the time a Columbia College undergraduate, hired to wash the dirty fly bottles. Just before washing one he noticed a fly with *white eyes.* Shine and Wrobel (1976, ch. 5) have a nice discussion of the possible origin of that *white-eyed* male but they are unable to reach any definitive conclusion.

FIG. 30. Calvin Bridges in the Fly Room, about 1926.

Morgan did not begin work with *Drosophila* in the hope of extending Mendelism to that small insect. Instead, he was more interested in problems of evolution, and especially that argument of long duration—continuous *vs.* discontinuous variation. He was especially interested in testing the mutation hypothesis of de Vries (1901–1903, 1906) and realized that a species with a short generation time, easily cultured, and with numerous offspring would serve his purpose.

The interval between Morgan's first paper (1910*a*) on the *white-eyed* fly and Bridges' paper of 1916 on non-disjunction saw the foundations of *Drosophila* genetics laid and the conceptual basis essentially completed—all in the Fly Room. This was to supply the critical evidence that, beyond all reasonable doubt, the Suttonian paradigm could be accepted as true. From 1916 until 1953 most work in genetics was the normal science that fleshed out the conceptual framework of the paradigm. Sturtevant (1965*a*) gives a lively account of those brave days. See also G. E. Allen (1978), Carlson (1981), and Shine and Wrobel (1976).

We will now discuss some of the monuments that emerged from the Fly Room.

LINKED GENES

Calvin Bridges (Fig. 30) is remembered as the person in the Fly Room with the sharpest eyes for detecting new mutants. The group soon had dozens for use in their experiments. One might ask, "Why study so many?" Once it had been established that the Mendelian scheme worked for alleles on the autosomes and, with modification, for alleles on the **X**, why pile confirmation upon confirmation? The answer was simple: the mutant alleles could be used as probes to gain more information about the physical basis of inheritance, *i.e.*, the relation of genes to chromosomes, the location of genes, the preparation of genetic maps of the chromosomes, and various alterations of the structure of the chromosomes themselves.

FIG. 31. The corner of the Fly Room where the fly food was made.

When Sutton started it all in 1903, he argued that there must be more pairs of alleles than there were pairs of homologous chromosomes.

> We must, therefore, assume that some chromosomes at least are related to a number of different allelomorphs. If then, the chromosomes permanently retain their individuality, it follows that all the allelomorphs represented by any one chromosome must be inherited together. (p. 240)

One cannot read the papers of this extraordinary young scientist without being in awe of the brilliance of his analysis. Note the proviso: the different alleles must be inherited together *if* the chromosomes retain their individuality. One suspects that when the peculiar ratios that were labelled "coupling" and "repulsion" were discovered, he would have recognized that they must somehow be associated with the presence of different genes in the same chromosome. And when coupling was not complete, he may well have realized that a mechanism must be sought to account for the observation that the chromosomes do not always retain their individuality.

It was obvious to those geneticists who accepted the Suttonian hypothesis, therefore, that the original Mendelian scheme could not account for the results when two or more pairs of different alleles were parts of the same pair of homologous chromosomes.

COUPLING AND REPULSION

Bateson, Saunders, and Punnett (1906, pp. 8–11) had not accepted Sutton's hypothesis and they had great difficulty in explaining some of their crosses that failed to give the usual Mendelian ratios. They noted that

> Early in the revival of breeding experiments, attention was called, especially by Correns, to the phenomenon of coupling between characters. Complete coupling has so far been most commonly met with among characters of similar physiological nature . . . . Examples of *partial* cou-

pling have not hitherto been adequately studied.

They then gave an example. In one of the experiments with sweet peas involving two pairs of alleles, a ratio of 7:1:1:7 was observed in the F$_2$.

In sweet peas *blue* (**B**) flower color is dominant to *red* (**b**). *Long* (**L**) pollen grain is dominant to *round* (**l**). When a *blue-long* was crossed with a *red-round*, all of the F$_1$ individuals were *blue-long.* Nothing surprising so far. In the F$_2$ one observed the usual ratio of 3:1 so far as *blue vs. red* and *long vs. round* are concerned. Since this is a cross involving two pairs of alleles, the normal Mendelian expectation would be 9 *blue-long* : 3 *blue-round* : 3 *red-long* : 1 *red-round.* Instead, the observed phenotypic ratios were roughly 7:1:1:7 in the order of the phenotypes just listed—hardly Mendelian.

Figure 32A shows the cross. The F$_1$ *blue-long* individual should have produced the four types of gametes as shown. In order to be sure that this was the case a test cross was made. That is, the F$_1$ individuals were crossed with the pure recessive as shown in Figure 32B. The expected results are indicated—25 percent each of the four phenotypes. But this is what happened:

	Expected	Actual
blue-long	25%	43.7%
blue-round	25%	6.3%
red-long	25%	6.3%
red-round	25%	43.7%

Although these are not the results expected from a dihybrid Mendelian cross, there must be some rule at work since, when the experiments were repeated, Bateson and his associates always observed the same results. The two rules seemed to be:

1. The most common phenotypes are those of the original parents and they are in the same frequencies—43.7 percent each (data given above for the Fig. 32B cross and 32C).
2. The two recombinant classes, *blue-round* and *red-long* are much less frequent than expected but their frequencies are equals, namely, 6.3 percent.

Somehow the alleles of the original parents are "coupled" in some manner and are more frequent than expected. Yet coupling is not complete and the alleles of the original parents may be "repulsed" and produce the recombinant classes.

This tendency for the different alleles to be coupled was confirmed by the cross of *blue-round* × *red-long* individuals (Fig. 32C). If these peas were playing by the Mendelian rules, one would expect this cross to be exactly the same as that of Figure 32A. The only difference is that the two pairs of alleles are distributed differently between the parents. The F$_1$ individuals have the same phenotypes (*blue-long*) and the same genotypes (**BbLl**).

When one of the Figure 32C F$_1$ individuals is crossed with the pure recessive, one would expect the same results as in the Figure 32B cross—after all the two F$_1$ individuals have the same genotype and phenotype. The results were dramatically different. The *blue-long* and *red-round*, which each had a frequency of 43.7 percent in the Figure 32B cross, have now dropped to 6.3 percent. The two other phenotypic classes have increased from 6.3 percent to 43.7 percent.

Bateson, Saunders, and Punnett were unable to provide a satisfactory explanation for these crosses. They could conclude only that, in crosses of this sort, the alleles of the parents were coupled. Coupling was not complete and in a small fraction of the gametes there was a repulsion of the two different alleles. Such an explanation, however, does no more than describe what in fact happens.

More and more examples of coupling and repulsion continued to be reported and no more than a formal explanation was possible. In the year that Morgan was to propose a satisfactory hypothesis Bateson and de Vilmorin (1911) wrote as follows (I have changed the genotypic symbols to those now used):

> If **A**, **a** and **B**, **b** are two allelomorphic pairs subject to coupling and repulsion, the factors **A** and **B** will repel each other in the gametogenesis of the double heterozygote resulting from the union **AAbb** × **aaBB**, but will be coupled in the gametogenesis of the double heterozygote resulting from the union **AABB** × **aabb** . . . .

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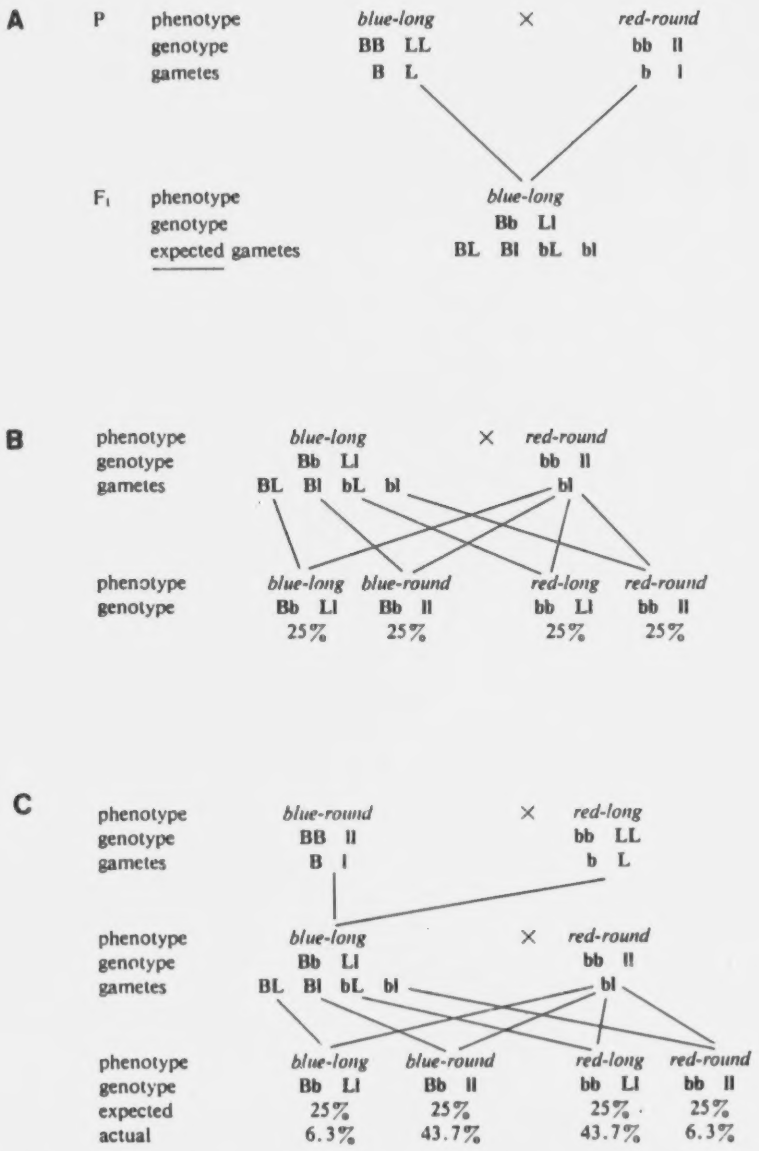


FIG. 32. Experiments with sweet peas. A shows the first cross and the gametes of the F_1 if there was independent assortment. B shows how the F_1 should have behaved if there was independent assortment. The expected frequencies, 25 percent for each, were not observed. Instead there were 43.7 percent each of *blue-long* and *red-round* and 6.3 percent each of *blue-round* and *red-long*. C is the reciprocal of A.

We have as yet no probable surmise to offer as to the essential nature of this distinction, and all that can be said is that in these special cases the distribution of the characters in the heterozygote is affected by the distribution in the original pure parents.

Bateson and his colleagues were not aficionados of Sutton's hypothesis but, as we

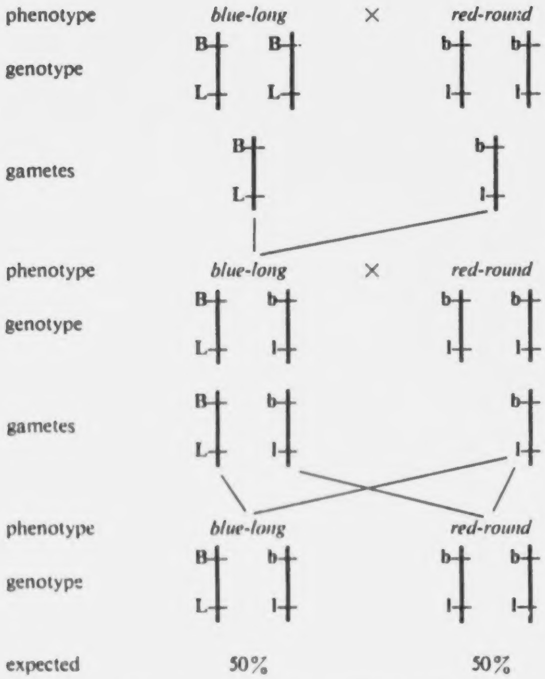


FIG. 33. An hypothesis to explain the cross of Figure 32A and 32B assuming complete linkage.

will see, unmodified Suttonism was no answer.

After seeing these results, and the admission of failure to offer an explanatory hypothesis, the faint hearted might have considered abandoning Mendelism as a broadly applicable hypothesis. Nevertheless, Mendel's rules did apply to many other crosses, even including the *blue vs. red* and *long vs. round* alleles when considered separately. Furthermore, the fact that constant, though mysterious, frequencies were observed suggested that there must be some constant and discoverable cause for them. Note also that in Figure 32B and 32C the alleles of the original parents were coupled. An orderly, though non-Mendelian, process appears to be at work. Could this be an example of Sutton's prediction for the behavior of different alleles that were part of the same chromosome?

WILL SUTTON'S HYPOTHESIS EXPLAIN COUPLING AND REPULSION?

We will assume that the loci for the alleles **B** and **L** are on the same chromosome and the *blue-long* parent in the cross of Figure 32A is homozygous for them as shown. We will assume that the other parent is homozygous for **b** and **l**. Figure 33 offers an explanation, such as Sutton might have proposed for the cross of Figure 32A and 32B.

When the F_1 *blue-long* individual is crossed with *red-round* the predicted offspring are of only two phenotypic classes: *blue-long* and *red-round*. However, that is not what was observed. Recall that the actual results were 43.7 percent for each of these two classes; in addition, 6.3 percent were *blue-round* and 6.3 percent were *red-long*. There is no possibility, however, of either of these less frequent classes appearing in Sutton's model as shown in Figure 33.

So the answer to the question at the head of this section appears to be "No." Nevertheless a modification of Sutton's hypothesis would eventually provide the answer.

In the buzzing activity of the Fly Room, Morgan and his associates were discovering dozens of new mutant flies. These new

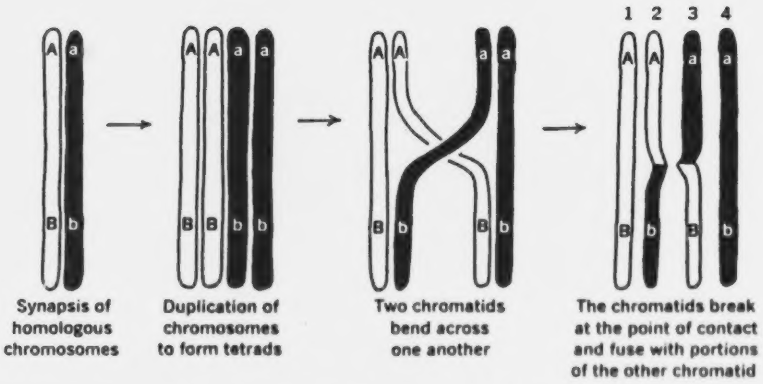

1
2
3
4
A
a
B
b
Synapsis of homologous chromosomes
Duplication of chromosomes to form tetrads
Two chromatids bend across one another
The chromatids break at the point of contact and fuse with portions of the other chromatid

FIG. 34. Janssens' hypothesis of crossing-over.

mutants were tested in crosses with other mutants. In many instances the dihybrid crosses gave the normal Mendelian 9:3:3:1 ratio in the F_2, which indicated that the two pairs of alleles were assorting independently.

Very quickly, however, problems arose; they were not unexpected. The reason was that, since *Drosophila melanogaster* has only four pairs of chromosomes, independent assortment of genes would be impossible, at the very latest, by the time the fifth mutant was discovered—there would be no remaining chromosome not already occupied by one of the previously discovered mutants. And, of course, independent assortment is possible only when the different genes are parts of different chromosomes.

Coupling and repulsion of the sort so puzzling to Bateson and his associates were observed in many of the *Drosophila* crosses. Sutton's hypothesis could explain the coupling but not the repulsion. Yet Morgan was convinced of the correctness of Sutton's hypothesis that genes are parts of chromosomes, so he assumed that there must be some mechanism whereby parts of chromosomes, with their alleles, could be exchanged.

Here was a case where the genetic data demanded a cytological explanation. One could imagine many ways that parts of chromosomes could be shuffled to provide an explanation for repulsion of different alleles. In fact, a cytological phenomenon had been described recently that might be the answer.

JANSSENS AND THE CHIASMATYPE THEORY

In 1909—the year before the birth of that *white-eyed* fly—the cytologist F. A. Janssens (1863–1924) had described a chromosomal phenomenon that Morgan required for his hypothesis.

The phenomenon that Janssens described is a meiotic event, now called crossing-over (Fig. 34). During synapsis the homologous chromosomes come close together with their long axes parallel. Both chromosomes replicate and a tetrad of four chromatids is formed. This much can be observed.

Next according to Janssens, there is considerable coiling of the chromatids around one another at this time and in some cases two of the chromatids break at the corresponding place on each. The broken chromatids rejoin in such a way that a section of one chromatid is now joined with a section of the other. As a result "new" chromatids are produced that are mosaics of segments of the original ones. The breaking and rejoining could not be seen so this event was but a hypothesis.

Janssens' Chiasmatype Theory is a case, not too infrequent in science, where the hypothesis turns out to be correct even though the supporting data were probably erroneous (McClung's hypothesis for the relation of the chromosomes and sex is an example).

The evidential basis for Janssens' hypothesis left much to be desired; nevertheless it was the only acceptable way to explain the data. This is E. B. Wilson's appraisal in 1925 (see also E. B. Wilson and Morgan, 1920):

> The basis for a more adequate cytological interpretation of crossing-over was first provided by Janssens' theory of the *chiasmatype* ('09) as elaborated by Morgan and his co-workers. Unfortunately this ingenious theory, though it may be correct in principle, still rests upon an inadequate cytological basis; it was, indeed, founded originally upon what now seems to have been a misinterpretation of certain cytological appearances. (p. 954)

MORGAN'S EXPLANATION FOR COUPLING AND REPULSION

In a one page paper Morgan (1911*b*) proposed a new hypothesis that, having been tested repeatedly, can be accepted today as true beyond all reasonable doubts. He started the analysis by noting that exceptions to the 9:3:3:1 ratio were being observed more frequently but that Bateson's hypothesis of coupling and repulsion was not a satisfactory explanation.

> In place of attractions, repulsions and orders of precedence, and the elaborate systems of coupling, I venture to suggest a comparatively simple explanation based on results of inheritance of eye color, body color, wing mutations and the sex factor for femaleness in *Drosophila.* If the materials that represent these factors are contained in the chromosomes, and if those factors that "couple" be near together in a linear series, then when the parental pairs (in the heterozygote) conjugate [*i.e.*, synapse] like regions will stand opposed. There is good evidence to support the view that during the strepsinema stage [when the tetrad begins to separate] homologous chromosomes twist around each other, but when the chromosomes separate (split) the split is in a single plane, as maintained by Janssens. In consequence, the original material will, for short distances, be more likely to fall on the same side of the split, while remoter regions will be as likely to fall on the same side as the last, as on the opposite side. In consequence, we find coupling in certain characters, and little or no evidence at all of coupling in other characters; the difference depending on the linear distance apart of the chromosomal materials that represent the factors. Such an explanation will account for all of the many phenomena that I have observed and will explain equally, I think, the other cases so far described. The results are a simple mechanical result of the location of the materials in the chromosomes, and the method of union of homologous chromosomes, and the proportions that result are not so much the expression of a numerical system [as Bateson proposed] as of the relative location of the factors in the chromosomes. *Instead of random segregation in Mendel's sense we find "associations of factors" that are located near together in the chromosomes. Cytology furnishes the mechanism that the experimental evidence demands.*

The term linkage was introduced for cases where different genes are parts of the same chromosome. Crossing-over, which occurs in meiosis, consists of the homologous chromosomes coming together at synapsis, replicating, then breaking, and finally the chromatids rejoining in new ways that result in altered associations of genes.

Thus, can we give credit to Thomas Hunt Morgan for having established that those puzzling exceptions to simple Mendelian inheritance are a consequence of the fact that genes are parts of the same chromosome and at times they are reshuffled by crossing-over during meiosis?

In truth, we can do nothing of the kind. All that could be concluded was that linkage *could* be an explanation of coupling and that crossing-over *could* be an explanation of repulsion. We credit Morgan with these important insights because later research showed that his hypothesis was correct.

AS.

This is a common pattern in the progress of our understanding of the phenomena of the natural world. The great hypotheses of the great men are those, among many competing hypotheses, that are eventually established by the work of numerous scientists as true beyond all reasonable doubt.

Morgan's realization that Janssens' hypothesis of chromatids breaking and rejoining in new combinations could explain the data was not readily accepted by other workers. It was impossible to observe directly such breakage and fusion. Sturtevant (1959) recalls why Janssens' hypothesis was so appealing:

> The cytological evidence was not conclusive, and the idea was not generally accepted—although it was becoming clear that only in some such way as this could the chromosomal interpretation of Mendelian inheritance be saved. (p. 294)

There was a way, however, to test the hypothesis that linkage is a consequence of different genes being parts of the same chromosome.

LINKAGE GROUPS AND CHROMOSOME PAIRS

By 1911 there was no longer any doubt that in diploid organisms the chromosomes are in homologous pairs, with the exception of the sex chromosomes where there might be deviations from this general rule. As noted before, Sutton (1903) had pointed out that "all the allelomorphs represented by any one chromosome must be inherited together." That means that the number of these groups of alleles inherited together cannot exceed the number of pairs of homologous chromosomes. Thus it would be possible to test this hypothesis in *Drosophila*.

Drosophila melanogaster has four pairs of chromosomes—three pairs of autosomes and a pair of sex chromosomes. In mitotic metaphase there are two pairs of long bent autosomes and one pair of tiny dot-shaped autosomes (Fig. 35). In females the two **X** chromosomes are rods of medium length and in males there is one **X** and a hook-shaped **Y**.

In the early months of experimentation, the Morgan group quickly found that a number of different genes were linked and that their pattern of inheritance suggested strongly that they were part of the **X** chromosome (Morgan, 1911*a*). Soon two other linkage groups were found (Morgan and Lynch, 1912; Sturtevant, 1913*c*). It was assumed that these were associated with the two pairs of long autosomes. So there were three linkage groups but four pairs of chromosomes. The discrepancy could have been due to the small size of the pair of dot autosomes—possibly consisting of only a few undiscovered genes or perhaps they are without any gene loci. The latter seemed to be the case for the **Y** chromosome.

Eventually one mutant fly was discovered and, when crossed with flies with mutant alleles of the three known linkage groups, there was independent assortment (Muller, 1914). It was highly probable, therefore, that this new mutant gene was part of the dot-shaped autosomes. Eventually other genes were discovered to belong to this fourth linkage group.

By 1915 the Morgan group had worked out the inheritance of 85 genes. These fell into four linkage groups as shown in Figure 35, which also shows a diagram of the metaphase chromosomes. The parallelism between the number of chromosomes, as determined by cytological examination, and the number of linkage groups, as determined by genetic experiments, was strong evidence not only that genes are parts of chromosomes but also that those that are parts of the same chromosome will be inherited together.

The data of Figure 35 are instructive in another way. Notice that many different genes affect the same character: 13 influence eye color; 33 modify the wings in some manner; 10 affect the color of the body.

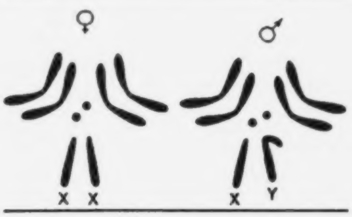
What, then, determines the normal red eye color? The answer is that the wild type alleles of all these 13 eye color genes, together with many discovered later and others yet to be discovered, act together to produce the normal wild-type red eyes. If an individual is homozygous for the mutant allele of any one of these genes, the

GROUP I

Name	Region Affected
Abnormal	Abdomen
Bar	Eye
Bifid	Venation
Bow	Wing
Cherry	Eye color
Chrome	Body color
Cleft	Venation
Club	Wing
Depressed	Wing
Dotted	Thorax
Eosin	Eye color
Facet	Ommatidia
Forked	Spines
Furrowed	Eye
Fused	Venation
Green	Body color
Jaunty	Wing
Lemon	Body color
Lethals, 13	Die
Miniature	Wing
Notch	Venation
Reduplicated	Eye color
Ruby	Legs
Rudimentary	Wings
Sable	Body color
Shifted	Venation
Short	Wing
Skee	Wing
Spoon	Wing
Spot	Body color
Tan	Antenna
Truncate	Wing
Vermilion	Eye color
White	Eye color
Yellow	Body color

GROUP IV

Name	Region Affected
Bent	Wing
Eyeless	Eye



GROUP II

Name	Region Affected
Antlered	Wing
Apterous	Wing
Arc	Wing
Balloon	Venation
Black	Body color
Blistered	Wing
Comma	Thorax mark
Confluent	Venation
Cream II	Eye color
Curved	Wing
Dachs	Legs
Extra vein	Venation
Fringed	Wing
Jaunty	Wing
Limited	Abdominal band
Little crossover	II chromosome
Morula	Ommatidia
Olive	Body color
Plexus	Venation
Purple	Eye color
Speck	Thorax mark
Strap	Wing
Streak	Pattern
Trefoil	Pattern
Truncate	Wing
Vestigial	Wing

GROUP III

Name	Region Affected
Band	Pattern
Beaded	Wing
Cream III	Eye color
Deformed	Eye
Dwarf	Size of body
Ebony	Body color
Giant	Size of body
Kidney	Eye
Low crossing over	III chromosome
Maroon	Eye color
Peach	Eye color
Pink	Eye color
Rough	Eye
Safranin	Eye color
Sepia	Eye color
Sooty	Body color
Spineless	Spines
Spread	Wing
Trident	Pattern
Truncate intensf.	Wing
Whitehead	Pattern
White ocelli	Simple eye

FIG. 35. The linkage groups of *Drosophila melanogaster* as known in 1915. The 85 genes fell into 4 linkage groups. The diagram at the lower left shows the chromosomes in somatic cells. (Morgan, 1915)

eye color will not be red but, instead, white, or peach, or sepia, etc. We should think of the normal red eye color as the end product of a series of gene actions. If any of these actions is altered, the eye color will be different.

It is important to realize also that there is more to the compound eye of an insect than its color. There are many other genes that influence the morphology of the eyes—some drastically as in the case of *eyeless* in the fourth linkage group or the *bar eye* mutant of the **X** chromosome.

The mutant alleles were named for their most viable effects—the *white-eyed* allele produces white eyes. When the *white-eyed* flies were carefully examined, however, it was found that the pigmentation of the ocelli and some of the internal organs were affected as well. This is not an unusual case—many genes are pleiotropic, that is, they affect more than one structure or process. Some geneticists in the early days even went so far as to suspect that every gene affects, at least in some small way, all aspects of structure and function of the body.

THE CYTOLOGICAL PROOF OF CROSSING-OVER

It was essential that Morgan's hypothesis of crossing-over as a mechanism to explain the recombination of linked genes be thoroughly tested, and if validation was not possible, that it be replaced. The hypothesis had been proposed to account for some exceptions to simple Mendelian inheritance; so the fact that the data verified the hypothesis could not be accepted as support for the correctness of the hypothesis.

The critical proof would be cytological evidence for the actual breaking and recombination of homologous chromatids. Such events were assumed to take place in meiosis during synapsis and tetrad formation. At that time the chromosomes were exceedingly difficult to study. The problem was further exacerbated by the fact that homologous chromosomes are identical in appearance, so even if crossing-over had occurred during synapsis, the chromatids would give no visible evidence that they had broken and recombined.

Ask your students to consider this difficulty and to suggest how an experiment might be designed to provide critical evidence. They might suggest that, since evidence cannot be gained when the homologous chromosomes are identical, it will be necessary to find a species with dissimilar homologous chromosomes or to make them different by experimental means.

In the 1910s there was no obvious way of making chromosomes different and the *Drosophila* group accepted the hypothesis of crossing-over because it continued to explain their data. In fact it was almost 20 years before Curt Stern (1931) was able to provide cytological proof of crossing-over.

By the time Stern began his work, *Drosophila* geneticists had a large number of stocks of mutant flies, including numerous ones with chromosomal abnormalities. Some of these had appeared "spontaneously" in the stocks in the Fly Room but others had appeared in cultures of flies that had been exposed to radium or X-rays.

There was a remarkably cooperative spirit among the *Drosophila* geneticists and they exchanged stocks with their fellow scientists in various institutions within the United States and throughout the world. For years the Morgan group, first at Columbia University and after 1928 when they moved to the California Institute of Technology, kept hundreds of stocks for their own use and for any geneticist requesting them. Subsequently a large collection was maintained at the University of Texas, and currently there is a National Drosophila Species Resource Center, supported by the National Science Foundation, at Bowling Green State University in Kentucky.

Stern constructed stocks that provided the test material that he needed—flies with structurally and genetically different homologous chromosomes. The females used had structurally and genetically different **X** chromosomes (Fig. 36 is a simplified representation of one of Stern's critical experiments). One of the **X** chromosomes was in two portions: one portion behaved as an independent chromosome and the other was attached to one of the tiny fourth chromosomes. The other **X** had a piece of a **Y** attached to it. These struc-

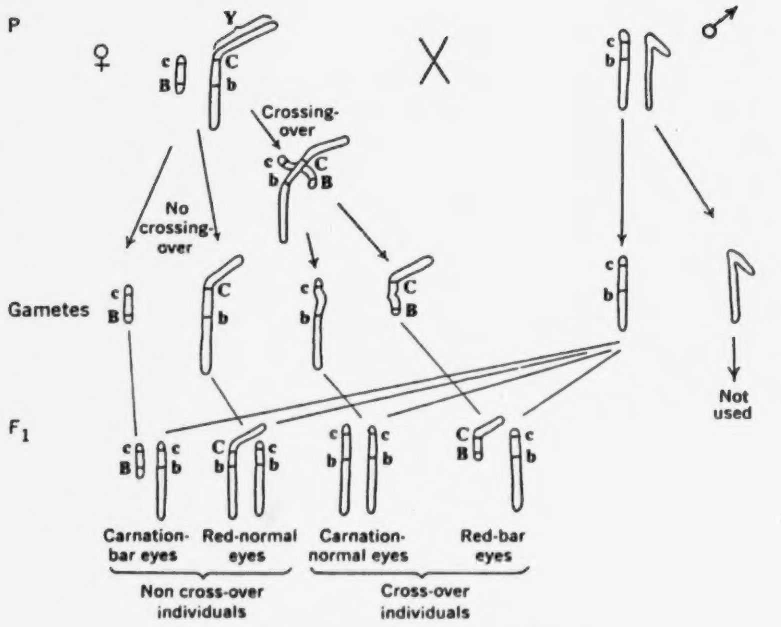


FIG. 36. Stern's cytogenetic proof of crossing-over.

tural differences were so great that it was possible to identify the chromosomes in fixed and stained cells.

The two **X** chromosomes carried genetic markers as well. One part of the divided **X** carried the recessive allele *carnation* (**c**), which when homozygous produces eyes of a dark ruby color, and the dominant allele *bar* eyes (**B**), which reduces the normal nearly round eyes to a narrow band. The **X** with the piece of the **Y** carried the *wild-type* alleles **C** and **b**, which produce *red* eyes and *normal-shaped* eyes.

During meiosis in the female there will be crossing-over between the two loci in some instances but not in others. As a consequence four types of eggs will be produced. Each of these is unique both genetically and structurally. When such a female is crossed with the double recessive, a *carnation normal-eyed* male, the alleles of each of the gametes of the female will be expressed.

The critical evidence was provided by the F_1 females, which would be in four phenotypic classes. Furthermore, each phenotypic class would have predictably different chromosomes. Stern had set up the cross in such a manner that the crossover individuals with *carnation normal-shaped* eyes would have two long **X** chromosomes. The other crossover class would have eyes that were both *red* and *bar*. Their chromosomes would show one long **X** and one **X** with the piece of the **Y**. The other two phenotypic classes, the non-crossovers, would also have unique chromosomal configurations.

Stern checked the chromosomes of nearly 400 of the females of all four classes and found that the phenotypes corresponded to the predicted cytological configurations. This was an elegant demonstration that Morgan's hypothesis of cytological crossing-over as the basis for genetic crossing-over was indeed correct.

And history was repeating itself. In a paper published a few weeks earlier Harriet Creighton and Barbara McClintock (1931) demonstrated that crossing-over has a cytological basis in corn (*Zea mays*). Their basic method was the same as that used by

Stern for *Drosophila*. They had developed strains of corn with genetically and cytologically different 9th chromosomes. Their evidence was the presence of predicted cytological configurations in the plants with the different phenotypes.

MAPPING THE CHROMOSOMES

Much of *Drosophila* genetics was anticipated in Morgan's first full length paper (1911*a*). It is interesting to note that, although nearly 50 pages in length, there are no references, just two footnotes mentioning earlier expressions of his ideas. One anticipation suggested was the possibility of preparing a genetic map of *Drosophila* genes. In this paper, dealing with the first mutant genes found on the **X**, Morgan noted that the data showed

> the necessity of assuming some . . . localization [of the genes] amongst some of the substances resident in the same chromosome. (p. 403)

He noted that Janssens' hypothesis would seem to require that

> the chromosomal materials that represent the factors of heredity are placed linearly along the chromosome and in corresponding linear series in each pair of homologous chromosomes. (p. 404)

Morgan noted also that for genes on the same chromosomes the

> associations will be more or less common according to the nearness of the associated factors in the chromosome. (p. 404)

In a very short paper that same year (1911*b*) Morgan is more definite:

> we find coupling in certain characters, and little or no evidence at all of coupling in other characters; the difference depending on the linear distance apart of the chromosomal materials that represent the factors.

These quotations stress two principal hypotheses: genes are localized in definite places in the chromosome, and they are in a linear order. If one assumes that crossing-over can occur at any place along a chromosome, the chance of one occurring in any one segment will depend on the length of that segment—the longer the segment, the greater the probability that crossing-over will occur somewhere within it. The discovery that the percentage of recombination ("repulsion") between any two genes on the same chromosome was constant suggested that some discoverable mechanism was in operation. Bateson and his associates had also observed this in their crosses.

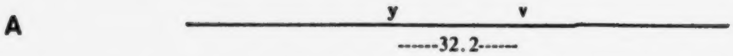
The first genetic map was produced by Sturtevant (1913*a*) as his Ph.D. thesis. He used five mutants and the corresponding wild type alleles that are on the **X** chromosome: *yellow* body (**y**), *white* eyes (**w**), *vermillion* eyes (**v**), *miniature* wings (**m**), and *rudimentary* wings (**r**).

Sturtevant accepted Morgan's hypothesis for the position of genes in chromosomes and made the following deduction:

> It would seem, if this hypothesis be correct, that the proportion of 'cross-overs' could be used as an index of the distance between any two factors. Then by determining the distances (in the above sense) between A and B and between B and C, one should be able to predict AC. For, if proportion of cross-overs really represents distance, AC must be approximately, either AB plus BC, or AB minus BC, and not any intermediate value. (p. 45)

Sturtevant then began the experiments in which he crossed flies with mutant alleles on the **X** with wild-type flies. The F_1 females were then crossed with males carrying the recessive alleles. (F_1 males were not used since Morgan had discovered earlier that crossing-over does not occur in them.) The offspring were then scored as to whether recombination of the alleles being followed had occurred. Such recombination would indicate that a cross-over had occurred between the loci.

The percentage of crossovers between **y** and **v** was found to be 32.2 and between **y** and **m** to be 35.5 percent. Morgan's hypothesis would suggest that **v** would be slightly closer to **y** than **m** would be. But what could be concluded about the relative positions of **m** and **v**? Sturtevant's predic-



Now **m** can be either to the right or to the left of **y**, as shown here:

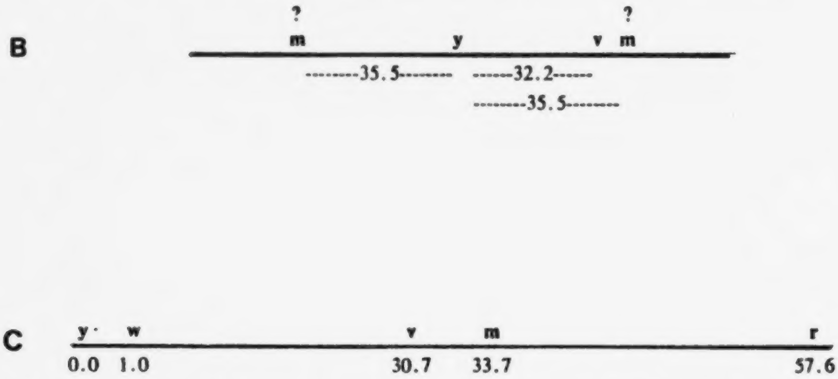


FIG. 37. Sturtevant's method for determining the linear order of gene loci. A shows **y** and **v** separated by a distance equal to the percentage of crossing-over between them. B shows the percentage of crossing-over between **y** and **m** and the impossibility of knowing whether **m** is on the side with **v** or not. C shows the relative position of five loci on the **X** chromosome.

tion was that the distance between **m** and **v** must be either 67.7 (35.5 + 32.2) or 3.2 (35.5 − 32.2).

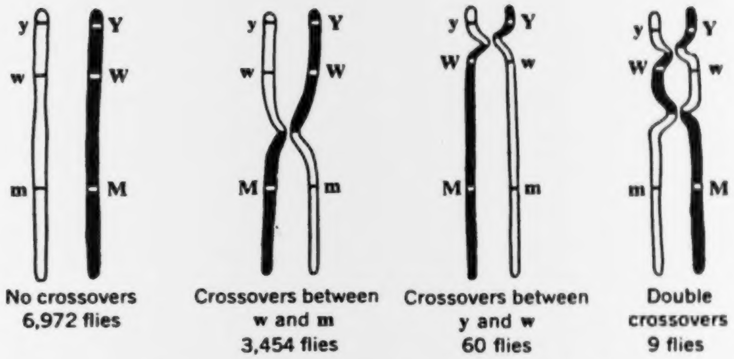
Presenting this argument in an illustration, such as Figure 37, may not be equal to a thousand words, but it is surely equal to a few hundred. We will represent the chromosome as a line and assume that its hereditary materials are linear in their arrangement. Morgan had no doubt adopted such a hypothesis because he was initially influenced by the shape of chromosomes—long threads, especially in prophase.

Figure 37A represents the data for crossing-over between **y** and **v**. The amount was 32.2 percent and, in drawing the figure, the two genes were put 32.2 mm apart. The second experiment showed that the percentage of crossing-over between **y** and **m** was 35.5. Now we have two choices since we have already put two points on our chromosome-line: **m** can be either on the same side as **v** or it can be on the other side of **y** (Fig. 37B).

If we assume the working hypothesis to be correct, in one case **v** and **m** would be very close to one another—only 3.2 units apart. In the other they would be 67.7 (35.5 + 32.2) units apart. The precise form of the hypothesis allowed a critical deduction and test to be made—measure the amount of crossing-over between **v** and **m**. Sturtevant did the experiment and found the value to be 3 percent. This indicated that **v** and **m** were close together and therefore on the same side of the chromosome relative to **y**. The close correspondence between the actual and expected results was strong support for the correctness of the hypothesis.

Sturtevant made similar crosses with the *white* eyes (**w**) and *rudimentary* wings (**r**) alleles and constructed the first genetic map, which is redrawn in Figure 37C. The **y** locus was taken as the starting point and the other gene loci placed at a distance equal to the percentage of crossing-over between adjacent loci.

A puzzle was soon encountered. Repeated experiments showed that the apparent distance between loci depended on how the genetic map was constructed. The map of Figure 37C shows the distance between **y** and **r** to be 57.6. This is the sum of the individual values for crossovers between **y** and **w**, **w** and **v**, etc. If the percentage of crossing-over was determined by actual



No crossovers
6,972 flies

Crossovers between
w and m
3,454 flies

Crossovers between
y and w
60 flies

Double
crossovers
9 flies

FIG. 38. Sturtevant's experiment. See text for details.

experiment using the two genes **y** and **r**, the value was found to be less than that predicted.

It would be interesting to ask students to suggest explanatory hypotheses to account for this puzzle. If they have trouble proposing hypotheses, mention that Sturtevant's own hypothesis was that double crossing-over might have occurred. This would put the alleles back in the same chromosome. The result would be an apparent lack of crossing-over between the two loci when, in fact, there had been two. Then ask the students how one could possibly test such a notion.

The answer is that the test experiment must involve at least three loci. In one experiment Sturtevant crossed individuals that had **y**, **w**, and **m** on one **X**, and **Y**, **W**, and **M** on the other with males with the three recessive alleles. He raised 10,495 offspring and by checking the phenotypes could test whether or not crossovers had occurred (Fig. 38). Thus, if there were no crossovers between **y** and **m**, the offspring would either have *yellow* bodies, *white* eyes, and *miniature* wings or be *wild-type*—in approximately equal numbers. He found this to be true of 6,972 flies, which were of these two phenotypes. If crossing-over occurred between the **w** and **m** loci, the flies would be either *yellow-bodied, white-eyed,* with *wild-type* wings or *wild-type* body and eye color but with *miniature* wings. Flies of these two kinds numbered 3,454. Crossing-over between the **y** and **w** loci would give flies that had either *yellow* bodies and both *wild-type* eye color and wings, or *wild-type* body color with *white* eyes and *miniature* wings. Only 60 flies were of these two kinds indicating that **y** and **w** are close to one another.

And finally there were 9 individuals, in the total of 10,495 that had *yellow* bodies, *wild-type* red eyes, and *miniature* wings or *white* eyes and *wild-type* body color and wings. These could be accounted for on the basis of double crossing-over, as shown in Figure 38.

It should be clear, therefore, that a minimum of three genes is necessary to detect double crossovers. If only the **y** and **m** loci had been used, any double crossing-over between them would have gone undetected since **y** and **m** would have resumed their original positions (Fig. 38, rightmost case). Because of the occurrence of double crossing-over, the workers in the Fly Room made their genetic maps by summing the data from crosses involving loci close together, not those that were far apart.

Is the genetic map, constructed in this manner, an accurate reflection of the positions of the genes on the chromosomes? Sturtevant has this to say (the genetic symbols have been updated):

> Of course there is no knowing whether or not these distances as drawn represent the actual relative spacial distances apart of the factors. Thus the distance **wv** may in reality be shorter than the distance **yw** but what we do know is that a break is far more likely to come between **w** and

> **v** than between **y** and **w**. Hence, either **wv** is a long space, or else it is for some reason a weak one. The point I wish to make here is that we have no means of knowing that the chromosomes are of uniform strength, and if there are strong or weak places, then that will prevent our diagram from representing actual relative distances—but, I think, will not detract from its value as a diagram. (p. 49)

Sturtevant reaches the following conclusion in his Ph.D. thesis:

> These results are explained on the basis of Morgan's application of Janssens' chiasmatype hypothesis to associative inheritance. They form a new argument in favor of the chromosome theory of inheritance, since they strongly indicate that the factors investigated are arranged in a linear series, at least mathematically.

An aside on presenting this topic to students. First-year students do not normally think in terms of the position of genes in chromosomes so the method used by Sturtevant to map the genes might present some difficulties. Nevertheless here, as with many problems in genetics, a more familiar metaphor may help the students to understand the problem as well as involve their reasoning powers. What I am about to propose will require more time for covering the topic but one can argue it may be better for the student to take that extra time and to understand the topic.

Assume that we have some data relative to a trip on Interstate 80 from New York to San Francisco and we wish to use these data to locate some of the cities *en route* and to find the distance between them. Assume also that the data given will be the only data available. Our first facts will be the distances, in kilometers, between these cities:

Chicago and New York	1,290
Chicago and Salt Lake City	2,592
Chicago and San Francisco	3,450
Chicago and Cleveland	540
Chicago and Cheyenne	1,536
Chicago and Omaha	740

Now ask "What is the distance from New York to San Francisco?" Hopefully some student will respond with 4,740, the sum of 1,290 and 3,450. Point out that the answer given assumes that we know the relative positions of Chicago, San Francisco, and New York. If we did not know that, it would be equally probable that the distance between New York and San Francisco is 2,160 kilometers (3,450 minus 1,290) if New York was between Chicago and San Francisco.

The students should then be asked to specify what additional sorts of information are required for the cities mentioned to be placed in their relative positions. This can be done, of course, without knowing whether San Francisco is north, south, east, or west of Chicago.

Now back to chromosomal distances. You may recall that in his address to the American Breeders Association, Morgan blasted the Mendelians for suggesting all sorts of unproven mechanisms to explain the exceptions to the original Mendelian rules. The same criticism was now to be turned on the Morgan group and it was to continue for some years: Was it permissible to imagine the chromosomes doing all these wonderful things, such as single and double crossing-over, when there is not the slightest cytological evidence for such events?

That was a difficult criticism to answer in the 1910s but the basic fact remained—as more and more data were accumulated they were found to "make sense" on the basis of the hypotheses being developed by the *Drosophila* group. They were providing a conceptual scheme that accounted for more and more of the phenomena of genetics. This, in itself, makes it more probable that the conceptual scheme is correct.

CAN TWO STRUCTURES OCCUPY THE SAME SPACE?

Here is another puzzle that will be profitable for your students to consider. When Sturtevant (1913*a*) conducted the experiments that led to the construction of the genetic map of the **X** chromosome, he identified the locus of the mutant *eosin*,

SEI
133

which when homozygous produces eyes colored like the cytological stain of that name. He also found that, so far as he could see, *eosin* and *white* gave the same crossover percentages relative to adjacent loci. How could that be? This problem was studied by Morgan (1912*a*, 1914*a*). By 1915 the answer seemed clear (Morgan, Sturtevant, Muller, and Bridges, 1915).

> The "distance" between them [white and yellow] is 1 unit, which means that crossing over takes place about once in a hundred times. Eosin eye color gives the same crossing over frequency with yellow. White eye color gives with miniature wings about 33 percent crossing over. Eosin gives the same value with miniature. White gives 44 per cent. of crossing over with bar eye. Eosin has the same value. Similar relations hold for all the characters of the first [linkage] group. (p. 156)

What is one to make of this? If crossover data can be used to determine the relative positions of genes in a chromosome, the information just given would seem to indicate that *eosin* and *white* occupy the same locus. Can this be? Some alert students may suggest that *eosin* and *white* may be so close together that one would have to count hundreds of thousands of flies in order to detect any crossing-over.

Next ask students what is the accepted explanation for a 3:1 Mendelian ratio.

Morgan, Sturtevant, Muller, and Bridges continue,

> 1. If a white-eyed male of Drosophila is mated to a red-eyed female, the F_2 ratio of 3 reds to 1 white is explained by Mendel's law, on the basis that the factor for red is the allelomorph of the factor for white.
>
> 2. If an eosin-eyed male is mated to a red-eyed female, the F_2 ratio of 3 reds to 1 eosin is also explained if eosin and red are allelomorphs.
>
> 3. If the same white-eyed male is bred to an eosin-eyed female, the F_2 ratio of 3 eosins to 1 white is again explained by making eosin and white allelomorphs. (p. 155)

Your students may be able to discover the concept of "multiple alleles" for themselves. If not, this is how the Morgan group explained the data.

> This example indicates that the conception of allelomorphs should not be limited to two different factors that occupy identical loci in homologous chromosomes, but that there may be three, as above, or even more different factors that stand in such a relation to each other. Since they lie in identical loci they are mutually exclusive, and therefore no more than two can occur in the same animal at the same time. On *a priori* grounds also it is reasonable to suppose that a factor could change in more than one way, and thus give rise to multiple allelomorphs . . . .
>
> On the chromosome hypothesis the explanation of this relation is apparent. A mutant factor is located at a definite point in a particular chromosome; its normal allelomorph is supposed to occupy a corresponding position (locus) in the homologous chromosome. If another mutation occurs at the same place, the new factor must act as an allelomorph to the first mutant; as well as to the "parent" normal allelomorph. (pp. 155–157)

As the years went by many more mutants were discovered that mapped at the same *white* locus. This is no longer an isolated case. Multiple alleles of the same gene are a common genetic phenomenon.

It should be emphasized, once again, how new insights into the mechanisms of heredity were obtained as the body of information about this one species increased. It was far more profitable for that very active group in the Fly Room to have concentrated their efforts on one species than for them to have studied the genetics of a dozen. With the extensive library of mutant alleles available as early as 1915, all sorts of questions could be asked and there was a good chance of obtaining acceptable answers. Years later the fact that *E. coli* received such concentrated attention meant that its biology was to become the best known of any species.

Consider the Ph.D. thesis of Calvin Bridges as an example of how the genome could be manipulated to supply critical answers to critical questions.

THE FINAL PROOF

During the last two decades of the 19th century, the hypothesis that the factors responsible for inheritance, whatever they might be, were associated with chromosomes was held by only a few prominent cytologists. That hypothesis was given new life by Sutton in 1903. In the 1910s the investigations on *Drosophila* by Morgan, Sturtevant, Bridges, and Muller made it increasingly probable that genes are parts of chromosomes, yet Bateson and many others remained totally unconvinced. It is Calvin Bridges who is credited with having provided the "final proof" for that hypothesis.

Now that Sutton's hypothesis is totally accepted, it is hard to understand the reluctance of geneticists in the years between 1903 and 1916 to "see the light." To be sure that "light" is brighter today than it was in the first two decades of the 20th century. Probably an important factor in their reluctance was the extraordinary rapidity with which astonishing data and concepts emerged from the Fly Room. In those decades the biological sciences moved slowly and it may be that even the most capable geneticists at other institutions had trouble digesting the data and coping with the concepts. Then too, the terminology and symbolism of the papers describing the *Drosophila* crosses were difficult to understand. Even today when one looks at the papers published by the *Drosophila* group between 1910 and 1920, it is difficult to know, without considerable study, what was done.

Another reason for resistance to *Drosophila* genetics seems to have been emotional. When I was at Columbia during the 1930s, memory of the Morgan group was still strong (Morgan, Sturtevant, and Bridges had moved to Cal Tech in 1928). I was told by those who had been at Columbia during the late 1910s and early 1920s that the *Drosophila* group was regarded as being rather abrasive by some biologists. This may well have been so. Scientists working in fields making rapid progress may be impatient and condescending to those doing their Kuhnian normal science at a slower pace. In the opinion of those Columbia zoologists in a position to know, a large factor in the acceptance of the work on *Drosophila* was due to E. B. Wilson. Though one of the giants in the biological sciences of the time, he was a gentle person, warmly regarded, and his opinions were highly respected. I never heard of an "enemy" of E. B. Wilson. According to their story, it was Wilson's firm belief in the correctness of the *Drosophila* work that accelerated its acceptance by the biological community as a whole.

CALVIN BRIDGES 1916

In presenting Bridges' experiments to students, it is important that the normal inheritance of sex chromosomes be thoroughly understood. Figure 39 provides a review. The chromosomes of the female are shown in large letters and those of the males in small letters. The **x** chromosome of the male is transmitted only to his daughters and his **y** only to his sons. The **X** chromosomes of the female are transmitted to both sons and daughters. Thus a daughter receives one **X** from her mother and one **x** from her father. The son receives his **X** from his mother and his **y** from his father.

Again, with all that intense work in the Fly Room, innumerable new mutants were discovered. One strain behaved in a most unusual manner. In a cross of a *white-eyed* female and a *red-eyed* male one would expect in the F_1 generation daughters with *red* eyes and sons with *white* eyes, nothing more (Fig. 27). However, Bridges found that there were some *white-eyed* daughters and some *red-eyed* sons. There was no way this could have occurred, given normal inheritance of the sex chromosomes. Those daughters with the *white* eyes could not have received the **X** of the father, since it carried the dominant allele for *red* eyes and its influence would have prevailed. Therefore these exceptional daughters must have inherited their sex-linked genes from the mother alone. The exceptional *red-eyed* sons demanded a similar explanation. Since their **X** chromosome could normally come only

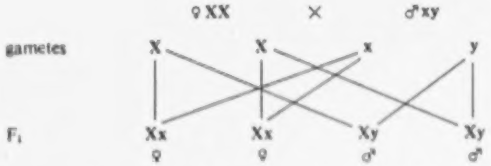


FIG. 39. The normal inheritance of sex chromosomes in *Drosophila melanogaster*. Female chromosomes in large letters and male chromosomes in small letters.

from the mother, and both of her **X**s carried the allele for *white* eyes, the **X** of the *red-eyed* male must have come from his *red-eyed* father.

What a mess. After four years of things seeming to work, it must have been most puzzling to encounter this strain of flies. But the point had been reached when the *Drosophila* group could be confident enough to treasure exceptions, since a phenomenon not explicable by the existing paradigm might, with further analysis, provide deeper understandings. But in order to save the paradigm, Bridges had to concoct a truly bizarre hypothesis to explain the data. Yet that bizarre hypothesis was capable of being tested.

The hypothesis Bridges proposed was that the female parent with the exceptional offspring had not only two **X** chromosomes but also one **Y**. During meiosis in this hypothetical **XXY** female, four classes of gametes were imagined to be produced: **X**, **XX**, **XY**, and **Y**. (A normal female would have produced only one class of gametes so far as the sex chromosomes are concerned—**X**.) There was no way of predicting the percentages of these gametes but experiments showed that 46 percent were **X**, 46 percent were **XY**, 4 percent were **XX**, and 4 percent were **Y**.

These **XXY** flies were called non-disjunction females. The term refers to the fact that in some of the ova there is no segregation, or disjunction, of the two **X** chromosomes and both remain in the ovum (a similar number would have gone into a polar body but, of course, polar bodies leave no progeny). In normal meiosis, one **X** would pass to the second polar body and the other **X** remain in the ovum.

One of the critical crosses made by Bridges is shown in Figure 40. It must have taken considerable courage to postulate this seemingly preposterous hypothesis yet, if one were to continue to maintain that genes are parts of chromosomes, some such hypothesis was required.

The fact of key importance in Bridges' hypothesis is that it could be tested, and hence its degree of preposterousness estimated. These are the main deductions:

1. If the hypothesis is true, we would expect 50 percent of the daughters to be non-disjunctional females (classes 1 and 7 of Fig. 40; the percentages shown in the figure are for all the flies so when females alone are being considered, the values should be doubled). All of the *white-eyed* females (class 7) should be non-disjunctional. The vast majority of the females were predicted to have *red* eyes (classes 1 and 2). These could not be distinguished by their phenotypes but, if used in genetic experiments, half would be normal (class 2) and half non-disjunctional (class 1). Bridges made the crosses and found that this deduction was true.

2. If the hypothesis is true, we would expect the exceptional males (class 4), that is, those males that inherited their **X** chromosome from their fathers, not to transmit the power of producing exceptional offspring in later generations. They were predicted to behave like normal males. They were tested and this was found to be true.

3. If the hypothesis is true, we would expect 46 percent of the males to be **XXY**. These would be expected to produce four types of sperm: **X**, **YY**, **XY**, and **Y**. Such a male crossed to a normal female should produce no exceptional offspring, that is, males inheriting their sex-linked characteristics only from the father and females inheriting theirs only from their mothers. However, every **XY** sperm entering a nor-

P Non-disjunctional white eye ♀ **XXY** × Normal red eye ♂ **XY**

Gametes **XY** (46%); **X** (46%) **XX** (4%); **Y** (4%) — **X** (50%) **Y** (50%)

F₁	**XY** (46%)	**X** (46%)	**XX** (4%)	**Y** (4%)
X 50%	1 **XXY** 23% Red eye ♀ Would show non-disjunctional behavior if crossed.	2 **XX** 23% Red eye ♀ Normal chromosome behavior.	3 **XXX** 2% Triploid X. ♀ Usually dies.	4 **XY** 2% Red eye ♂ The X has come from the father and the Y from the mother. This is the reverse of the normal situation.
Y 50%	5 **XYY** 23% White eye ♂ With extra Y chromosome.	6 **XY** 23% White eye ♂ With normal chromosome behavior.	7 **XXY** 2% White eye ♀ Would show non-disjunctional behavior if crossed.	8 **YY** 2% Dies

FIG. 40. Bridges' experiment with non-disjunction females.

mal egg with its single **X** would produce an **XXY** daughter. She would be non-disjunctional. This was tested and the predictions verified. That last short sentence gives no notion of the huge amount of work involved in this test as well as the others.

4. If the hypothesis is true, we would expect that 50 percent of the daughters (classes 1 and 7) would be **XXY**. This deduction was tested by making slides of the chromosomes of many of the females. Figure 41 shows what was found. Approximately half of the females (*a*) had the normal chromosome set with two **X**s. The other half (*b*) had the normal autosomes but two **X**s and one **Y**.

These were demanding deductions and elegant tests. Young Bridges concluded

> there can be no doubt that the complete parallelism between the unique behavior of the chromosomes and the behavior of the sex-linked genes and sex in this case means that the sex-linked genes are located in and borne by the X-chromosomes.

That is a brave, though properly restricted statement. The only thing the experiments had shown was that, at the time they were conducted, it was true beyond all reasonable doubt that the *white* and *red* alleles were parts of the **X** chromosomes in the strain of *Drosophila melanogaster* used in the experiments.

What, then, is the basis for claiming that these experiments were the final proof that genes are parts of chromosomes—implying that this is true for all genes in all species at all times? Had this been the first genetic experiment done with any organism, Bridges' conclusion just quoted would have been as much as could be said. But it was not the first. In the sixteen years since 1900, an enormous amount of genetic information had accumulated. Many species of animals and plants, each far from being unique, showed a pattern of inheritance that appeared to be based on simple rules. In fact, there was an underlying uniformity of genetic systems among the species in contrast to the vast differences in their structure and physiology.

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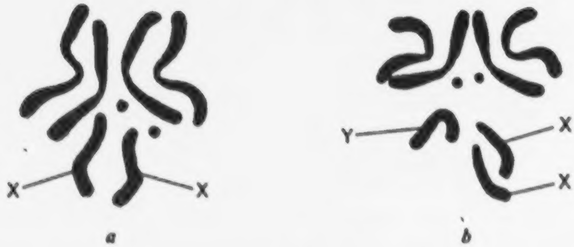

FIG. 41. Bridges' drawings of the chromosomes of female offspring in the cross shown in Figure 40. Approximately half of the females checked had the normal chromosomal complement shown in *a*. These would have been class 2. The remaining females (classes 1 and 7) were **XXY**. (C. Bridges, 1916)

Bridges was adding to the Theory of Genetics—to the entire body of data, hypotheses, and conclusions about inheritance. He was not challenging some well established paradigm. He was supporting that paradigm with a truly elegant proof.

Thus it was reasonable to extend the conclusion based on non-disjunction experiments to the other genes of *Drosophila melanogaster* and to genes of other species and conclude that in all species genes are parts of chromosomes.

Bridges' final proof in 1916 that genes are parts of chromosomes, which started on page 1 of volume 1 of the new journal *Genetics,* was a culmination of a series of investigations at Columbia University begun by Sutton in a laboratory on the same floor in Schermerhorn Hall. Sutton had stressed the parallelism of changes in chromosomes and Mendelian factors as indicating that the factors are probably associated with chromosomes. Wilson had corrected McClung's original misinterpretation of sex chromosomes and had gone on to produce his classic *Studies of Chromosomes.* At frequent intervals he published cautious updates on what was known of inheritance. Morgan, more interested in evolution than in heredity, had bred *Drosophila* to see if he would find similar abundant mutations, with striking phenotypic effects, that de Vries had reported for *Oenothera.* He did not find those de Vriesian mutations but, after many months, he did find the *white-eyed* male. Two Columbia undergraduates, Sturtevant and Bridges, began to work in Morgan's lab and soon Muller joined them. From then on the fate of classical genetics was sealed.

One can only speculate what the history of genetics might have been had those talented individuals not been in the same place and within the same decade—and after 1909 all working on that one tiny species, except for Wilson who was doing cytological work that was basic to genetic conclusions.

Now to another Columbia legend, which involves Bateson's visit to the Fly Room in 1921. One of the main events was a demonstration by Bridges of the chromosomal preparations from the non-disjunction experiments. Bateson, who knew next to nothing about cytology, is said to have gone from microscope to microscope dropping ashes from his pipe over everything. Eventually he announced that he was convinced that genes were parts of chromosomes. However, so the story goes, Bateson went to the AAAS meetings in Toronto and largely rescinded his acceptance of the chromosomal theory of heredity. G. E. Allen (1978, pp. 275–276) has a more complete and probably a more accurate account of Bateson's visit to Columbia.

In truth Bateson (1922) was most generous in his lecture in Toronto:

> We have turned still another bend in the track and behind the gametes we see the chromosomes. For the doubts—which I trust may be pardoned in one who has never seen the marvels of cytology, save as through a glass darkly—can not as regards the main thesis of the Drosoph-

> ila workers, be any longer maintained. The arguments of Morgan and his colleagues, and especially the demonstration of Bridges, must allay all skepticism as to the direct association of particular chromosomes with particular features of the zygote. The transferable characters borne by the gametes have been successfully referred to the visible details of nuclear configuration.
>
> The traces of order in variation and heredity which so lately seemed paradoxical curiosities have led step by step to this beautiful discovery. I come at this Christmas Season to lay my respectful homage before the stars that have arisen in the west.

THE MALE—MORE OR LESS?

These experiments on *Drosophila* plus those on many other species showed that the sex of an individual is determined by the sex chromosomes it receives when the ovum and sperm combine at fertilization. (We now know this is not true for all species.) Your students may have concluded that the full explanation of sex determination is at hand when, as in *Drosophila* and *Homo sapiens,* the zygote contains either **XX** or **XY**. But did any of your students inquire further? Is a female a female because she as two **X** chromosomes or because she has no **Y**? Is a male a male because he has a **Y** or because has has only one **X**? Or is sex determination the consequence of more complex phenomena?

If students are asked to suggest how such hypotheses could be tested, their proposals might not come readily. How can one juggle the chromosomes in ways that would provide tests of deductions? After learning about Bridges' experiments with **XXY** females, students might suspect that *Drosophila* could provide the material for answers.

Two bits of evidence have already been given that would provide a clue. The first is that in some species males are **XO**, that is they have only a single sex chromosome. The second datum is that, for the most part, the **Y** chromosome of *Drosophila* is genetically inert. Thus, one could argue that in the course of evolution the **Y** has become progressively less important, and finally in some species it has been totally eliminated.

Therefore, the hypothesis that males are males because they have only one **X** and females are females because they have two, has some support.

This hypothesis was strengthened by some remarkable flies that appeared in the Fly Room—they were female on one side of the body and male on the other. Similar individuals, known as gynandromorphs, had been observed in other species. Detailed analysis had not been done however, and the underlying cause remained unknown.

Males and females in *Drosophila* differ externally in several ways. The males have groups of bristles, the sex combs, on the forelegs and the posterior portion of the abdomen is solid black, whereas it is barred in the females. The genitalia of the two sexes differ considerably. In addition, males are smaller than females.

Cytological study indicated that these gynandromorphs began as normal **XX** females but, through some cytological accident at the very beginning of development, one of the **X** chromosomes was lost from a cell in part of the embryo. The descendents of this cell would have only a single **X** and, hence, have the genotype of a male. As a consequence, some individuals developed that were male on one side of the body and female on the other. The male side had the sex combs and the solid black posterior abdomen. The difference in body size resulted in this gynandromorph having a bent body—the larger female side bent the body considerably, making the male side concave. The genitalia were typically male on one side and abnormal on the female side.

Various sorts of gynandromorphs were observed depending on the time in development when the **X** chromosome was eliminated and the region of the embryo where it occurred. Not all were bilateral. The most interesting were those of known pedigree where the two **X** chromosomes had different alleles. One spectacular class of bilateral gynandromorphs were those with the allele for *red* eyes on one **X** and the allele for *white* eyes on the other. The result was an individual with a *red* eye on one side and a *white* eye on the other.

The hypothesis that an individual *Drosophila* was male or female depending on the number of **X** chromosomes in its cells was made highly probable by these observations. Through some accident of development there had been a juggling of the chromosomes and an important test of deductions had become possible.

The work of Bridges on non-disjunction (1921, 1939) showed that accidental events were producing even more striking chromosomal variations. As a consequence it became feasible to test in new ways the relation of the number of **X** chromosomes to the sex of the individual.

As we have seen, Bridges' **XXY** fly (Fig. 41) was a structurally normal and fertile female. She was among the first of many individuals discovered in the Fly Room that had abnormal chromosomes. After careful study Bridges gradually came to believe that sex was not determined solely by the number of **X** chromosomes (his data suggested little role for the **Y**) but by some relation between the **X**s and the autosomes. The following is a simplified version of his hypothesis.

Recall that a *Drosophila melanogaster* female has three pairs of autosomes and two **X**s (Fig. 35). We will use the term "autosomal set" and the letter **A** to apply to the monoploid group of autosomes—one of each homologous pair. The normal female, therefore, will have two sets of autosomes and a pair of **X**s. The ratio of **X**s to sets of autosomes will be 2**X**/2**A** = 1.0. The male will have a single **X** and two sets of autosomes. His ratio will be 1**X**/2**A** = 0.5.

A female was discovered that proved to be triploid—three of each kind of chromosome. What would that extra **X** do? A superfemale? Not at all. She was normal, and on the scheme just described, she would be 3**X**/3**A** = 1.

It seemed, therefore, that the ratios 1.0 = female and 0.5 = male was the rule. Were other combinations possible?

Once a fertile triploid female was available, the possibility of creating chromosomal havoc was at hand. Such a female crossed with a diploid male would produce various sorts of abnormal chromosomal combinations. If any of these new combinations were fertile they could be used in crosses to further perturbate the chromosomal system.

Some of the various combinations are shown in Figure 42. So long as the number of **X** chromosomes equals the number of autosomal sets, the ratio is 1.0 and the fly is a female. If a fly has two **X** chromosomes but 4 sets of autosomes then the ratio is 0.5 and its sex is male. Thus **XX** = female is true only if there are also two sets of autosomes.

But what would happen if the ratio were between 0.5 and 1.0? The extraordinary thing is that such a question could be asked and answered. The answer was that such flies are intermediate in their sex characteristics. They are called intersexes.

It was possible also to increase the ratio to values higher than 1.0 by having more **X** chromosomes than autosome sets. These flies, often called superfemales, tended to have the female characteristics exaggerated.

The combinations shown in Figure 42, plus others, were obtained and Bridges recognized a consistent pattern. Sex, far from being determined by genes of the "sex" chromosomes alone, is the result of interactions between genes on the **X**s and genes on the autosomes. The autosomal genes have a net male-forming tendency and the **X** chromosomes a net female-forming tendency. In a normal male the genes of the two autosomal sets overbalance the genes of the single **X**. In the normal female the double dose of genes provided by the two **X**s overbalance the genes on the autosomes.

Seemingly *Drosophila* genes and chromosomes could be altered to answer even the most difficult questions.

THE ORIGIN OF NEW MUTANTS

De Vries' (1901–1903, 1909–1910) report of frequent appearance of mutants in *Oenothera* stimulated many geneticists and evolutionists to search for them in other organisms. As noted earlier, Morgan

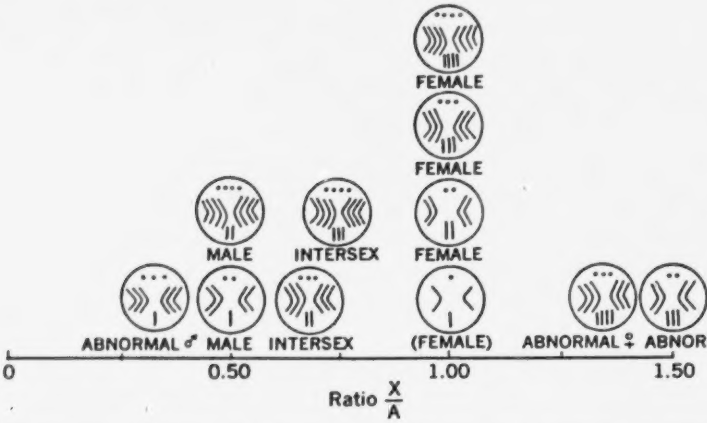

FIG. 42. The various combinations of **X** chromosomes and autosomes obtained by Bridges and others. The lowest circle at ratio 1.00 is a monoploid female. Bridges did not observe such an individual but some diploid flies were discovered to have monoploid areas in their bodies. If such areas happened to include sex structures, they were of the female type.

had started breeding *Drosophila* with that purpose in mind.

If one searches for mutants of *Drosophila*, or any other organism, merely by keeping a culture going and examining the individuals of each new generation, new mutants are exceedingly rare. *Drosophila* with *white eyes* or *vestigial wings* are encountered only when thousands of individuals are examined. Morgan wrote in 1914*a*:

> In fact, our experience with *Drosophila* has given us the impression that mutations are rare events, although the actual number of our mutations is now quite large.

There are two main reasons for this: the rarity of mutation at any locus and the recessiveness of nearly all mutant alleles. As a consequence nearly all mutant alleles are carried in the heterozygous state and masked by the dominant wild-type alleles. Your students will come to understand the problem if you ask them to devise an experiment for detecting mutant alleles. We will assume that a single recessive allele occurs in one heterozygous individual in a population of 1,000 flies. How would your students go about discovering it? They will soon conclude that a very large number of crosses would have to be made and a very much larger number of individuals have to be checked.

During the first decade of the 20th century, organisms were treated in various ways in the hope of increasing the rate of mutation. Morgan injected various chemical substances into different species of insects with the hope of obtaining mutants (G. E. Allen, 1978, p. 148). Later he exposed *Drosophila* to radium. The idea for this may have come from his Columbia colleague, James Howard McGregor, who was one of the first to test the effect of radium radiations on living organisms—he used frog gametes and embryos. Later Muller's work demonstrated that X-rays could indeed induce mutations.

The fact that some of Morgan's first cultures of *Drosophila* had been exposed to radiations makes it remotely possible that some of the mutants first discovered were radiation-induced. Morgan (1914*a*), however, did not believe that radiations had been the cause and subsequent experiments using radium and X-rays seemed not to produce mutations. Morgan (1914*b*) also wondered if etherization of the flies could cause mutations but could not find that it did.

E. B. Lewis (personal communication) believes that it is most unlikely that the swarm of mutants encountered in the Fly Room was radiation-induced. One reason is the very low dosages of radiations that would have been available to Morgan.

Lewis suspects the cause was hybrid dysgenesis(Lewin,1985,pp.626–627)brought about by crossing numerous different strains of *Drosophila melanogaster* caught in the wild. If this explanation is true it means that the advent of *Drosophila* genetics was a highly improbable event. If Morgan had used only a single culture, whether from Lutz, Castle, Payne, or caught personally, hybrid dysgenesis would not have occurred and there would have been no swarm of mutants.

Nevertheless once that original *white-eyed* male had been discovered, other mutant alleles were found. In just a few years the number had risen to 85 (Fig. 35). The unusual ability of Calvin Bridges to spot variations from the normal wild type played a large role in their discovery. But all in the Fly Room were active and successful in discovering mutant alleles. Sturtevant discovered many new mutant alleles even though he was color-blind. A near astronomical number of flies was examined and one suspects that the dedication, focus, and discipline of those working in the Fly Room were the major reasons that so much was discovered in such a short time.

INDUCED MUTATIONS

The nature and causes of the mutation process were of great interest not only to geneticists but to evolutionists as well. Were the sorts of inherited changes being studied in the Fly Room the basis of the variability required for Darwinian evolution? No one thought that mutational changes would be of such magnitude that a cytological examination of chromosomes would reveal them. But if the physical nature of the change could not be detected, possibly the process of mutation itself could be studied. That might become feasible if mutations could be produced by experimental means.

None of the early experiments to induce genetic changes was conclusive because of the difficulty of distinguishing induced mutations from spontaneous ones and because of the inadequate design of the experiments. Mutants appeared in stocks not exposed to the putative mutagenic agents. Their appearance could not be correlated with any known cause so they were termed "spontaneous mutations." They were rare. In experiments attempting to produce mutations by physical or chemical means, mutations occurred but also rarely. Thus, if we expose *Drosophila* to radium in the hope of producing mutations, and if a mutant fly appears in the F_1 or F_2 or later generations, we cannot be sure whether it is spontaneous or induced.

Since new mutant genes appear infrequently and nearly all are recessive, their detection poses a problem—as your students will have realized if they tackled the problem suggested at the beginning of this section. Assume, for example, that one autosomal gene in a sperm nucleus mutates. If this sperm then enters an egg—a highly improbable event in itself—the new individual will have one mutated allele from the father and the normal, and surely dominant, allele from the mother. The observer checking the offspring for new mutants will not recognize that this one fly in the group has a new mutant allele since it will be in the heterozygous state.

Appropriate crosses could have been made to produce the desired individuals homozygous for the mutant allele if there was some way of identifying the original heterozygote. Since there was no way of knowing this, the alternative would have been to make innumerable crosses in the hope of including that one heterozygote. This procedure was impractical for those interested in obtaining quantitative data on the production of new mutants.

MULLER'S **ClB** Method

H. J. Muller (1927) was the first person to give a practical solution for this problem. He devised an ingenious experiment that provided a simple, yet accurate, measure of mutation rate. He wished to compare the spontaneous mutation rate with the rate after exposing *Drosophila* to X-rays.

Muller developed a special strain of flies, known as **ClB**, that would enable him to measure the rate of mutation to a lethal state of any of the **X** chromosome genes.

A **ClB** female has one of her **X** chro-

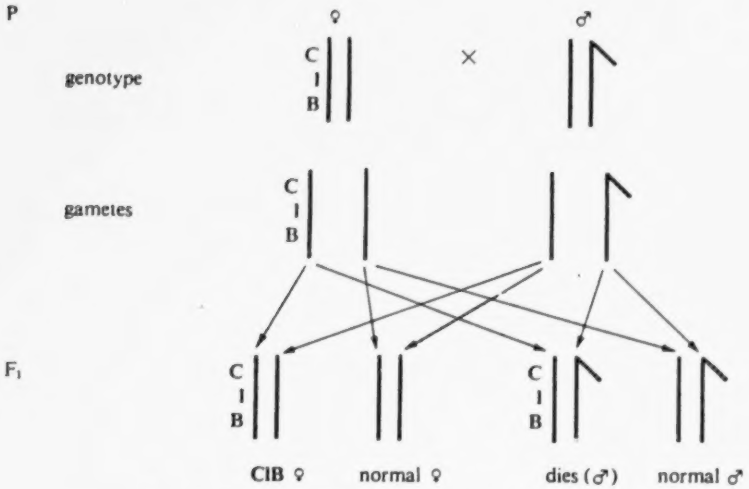

FIG. 43. Muller's **ClB** method. See text for details.

mosomes with an inversion designated **C**, a recessive lethal allele **l**, and the dominant *bar-eyed* allele **B**. The loci of both **B** and **l** are within the inverted region **C**.

An inversion is a region of the chromosome that has been reversed. If the normal order of hypothetical loci is **abcdefg**, a chromosome with loci in the order **abedcfg** would contain an inversion. Inversions are formed when a chromosome breaks in two places, in this case between **b** and **c** and **e** and **f**, followed by the rotation of the central piece and its fusion with the broken ends of the original chromosome. In this case the section **cde** rotates 180° and fuses with **b** and **f**.

By 1915 *Drosophila* workers were observing that some stocks showed very much reduced crossing-over between specific loci. Since crossover percentages were so important in locating the gene loci, this deviation was of concern. The cause was unknown but, since it was inherited, it could be studied. The "thing" causing the reduction in crossing-over was called a crossover suppressor. Sturtevant suspected that it might be an inversion, and in 1926 presented genetic data making that hypothesis probable. It was assumed that crossing-over was suppressed because in meiosis the two homologous chromosomes could not synapse in the region of the chromosomes where one homologue would have the normal sequence of loci and the other would have the sequence reversed (Fig. 46).

Muller had constructed his **ClB** stock with **B** and **l** within the **C** inversion knowing that they would remain linked, since no crossing-over would occur to separate them. The dominant **B** allele had the sole purpose of serving as a ready means of recognizing females heterozygous for the **ClB** chromosome. Homozygous females, with their two **ClB** chromosomes, would die, since there would be no normal allele to counteract the effects of **l**. Any male inheriting a **ClB** chromosome would also die, since there is no allele on the **Y** to counteract the effect of **l**.

Figure 43 shows what happens when a female heterozygous for a **ClB** chromosome is crossed with a wild-type male. Half of the daughters will be normal, and half will have *bar eyes* and hence carry a **ClB** chromosome. The sons inheriting the **ClB** chromosome will die because they have an unopposed **l** allele. The sex ratio, therefore, will be 2 females : 1 male.

Lethal genes on the **X** of *Drosophila* were first recognized by Morgan (1912*b*) when he encountered a stock that gave this 2:1 sex ratio. This was found to be due to a lethal allele carried by the females in the heterozygous state. Ask your students if it would be possible for homozygous females to be formed even if they would die. They may find it impossible to cross a heterozygous **ClB** female with a (deceased) **ClB** male.

At the time Muller was doing these experiments it was well known that many separate gene loci can mutate in such a way as to cause death. These lethal genes were nearly always recessive. Since many different loci can mutate to the lethal state, the chance of getting some one lethal mutation is greater than the chance of getting a specific mutation at a specific locus. Thus, if we studied the rate of mutations to the lethal condition on the **X** chromosome, we would be measuring the sum of the rates for *all* loci that could change in such a way as to lead to death in the male offspring. The number of such loci would be large but unknown.

The **ClB** stock allowed Muller to measure the frequency that some locus on the unmarked **X** will carry a lethal allele. First he wished to determine the normal rate of such mutations. With that information as a baseline, he could then try the effects of putative mutagenic agents—such as X-rays.

Figure 44 shows the experiment. What is being measured is the frequency with which a mutational change to the lethal condition has occurred in some one of the alleles on the **X** of the P generation male. The * indicates the presence of such a mutation.

This **X** of the male will be transmitted to the daughters. Thus the **ClB** daughters will have one **X** with the new lethal mutation and one with **ClB**. At this point it will almost surely be necessary to explain to some students why this female does not die—after all, she does have a lethal in each **X**. It is hard for some students to understand that in this case the lethal in one chromosome is not at the same locus as in the other and that each lethal allele has a normal allele on the other homologous chromosome. The confusion arises since both mutants have the same name—"lethal."

The F_1 **ClB** females are now crossed with normal males, as shown in the bottom of Figure 44. The daughters will be of two classes. Half will be **ClB** and the other half normal, though carriers for the new lethal. There will be no males. Half of the males would have died because they received the **ClB** chromosome and the other half because they received the **X** with the new lethal mutant.

Although *Drosophila* is a small fly, it is possible to distinguish males from females with the unaided eye. Thus, Muller could check his culture tubes rapidly to see whether or not males were present. It was then possible to ask "What is the frequency with which *some* locus on the **X** chromosome mutates to a lethal allele?"

The percentage was suspected to be very small, so thousands of crosses had to be made. Muller found that approximately one cross in a thousand, 0.1 percent, gave only females. This is the spontaneous mutation rate. Once again, this is not the rate for a single gene but for all the genes on the **X** that can mutate to a lethal state.

Although Morgan and other workers a decade earlier had concluded that X-rays would not induce mutations, Muller now found that they did. If males were exposed to about 4,000 r-units of X-rays, approximately one cross in ten gave only females—a mutation rate 100 times the spontaneous mutation rate.

Not only were these data inherently important but Muller had shown that X-rays were a convenient means of inducing mutations—not all of which were lethal, of course. In fact it was found that X-rays would induce not only gene mutations but also cause inversions, translocations (the transfer of a portion of one chromosome to another chromosome—as in Stern's experiment of Fig. 36), or deficiencies (elimination of a section of a chromosome). The chromosomes and genes of *Drosophila* could now be modified in complex ways that would allow geneticists to answer many questions not otherwise possible.

Apart from the importance of the data and the conclusions, we should not lose sight of the fact that Muller's **ClB** method was extraordinarily ingenious. He had constructed the genome of the **ClB** flies in such

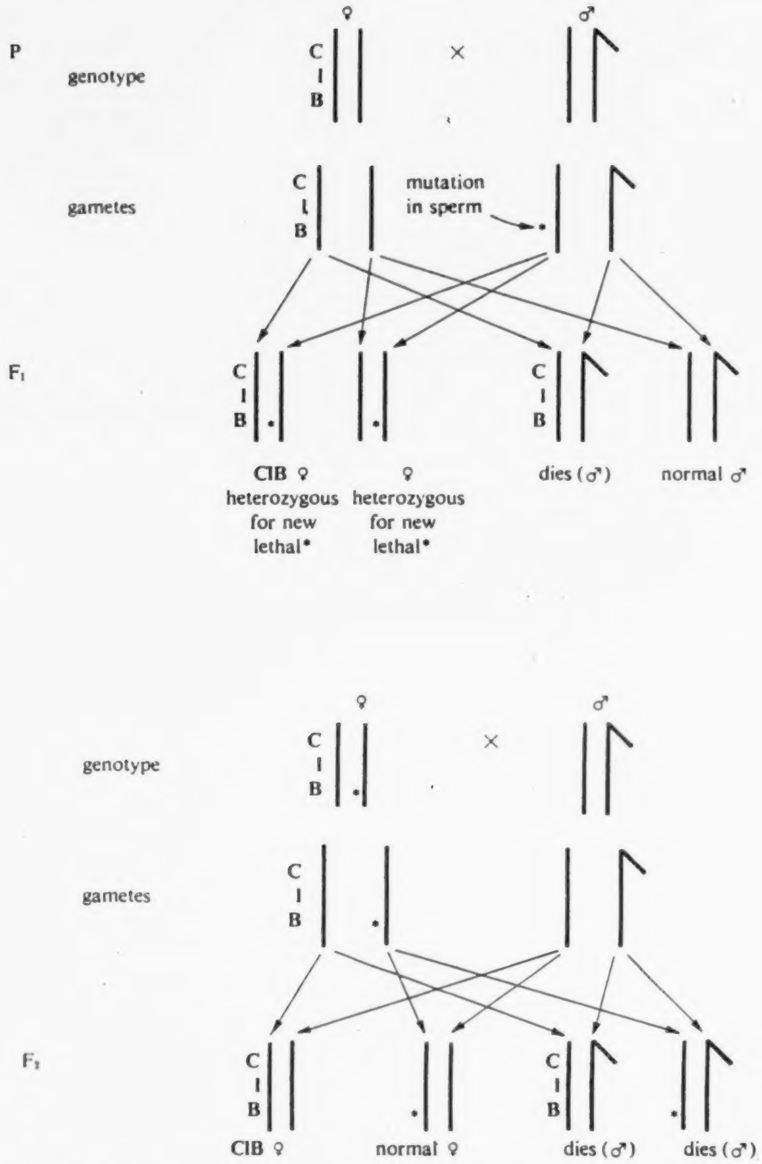

FIG. 44. Muller's **ClB** method used to detect lethal mutations. See text for details.

a way that he could measure the occurrence of a very infrequent phenomenon. In many instances, *Drosophila* could be molded to the needs of an experiment—at least in the hands of a genius. Once he could measure the spontaneous mutation rate accurately, he could then determine the mutagenicity of various external conditions. This was the beginning of a line of experimentation that is so very important to us today—the detection of environmental hazard, such as radiations and toxic chemicals, that induce mutations. We now live in such a hazardous environment that monitoring it is now a common public health practice.

SALIVARY GLAND CHROMOSOMES

The concepts of genetics were developed mainly on data derived from breeding experiments, with an occasional assist from cytology. Cytology provided gross confirmations: the number of homologous chromosome pairs equal to the number of linkage groups; chromosomes correlated with the sex of the individual; chromosomal behavior adequate to explain segregation and independent assortment. The usefulness of cytology was severely restricted, however, because available techniques were not sufficient to reveal the fine structure of chromosomes. If genes are in a linear order, it would be extremely useful to be able to recognize linear differentiations of the chromosomes.

Until the 1930s, however, the standard cytological techniques showed the chromosomes, with few exceptions as uniformly-staining structures, with no differentiations that could be associated with genes. The working hypothesis of geneticists was that genes were probably proteins. If so, it would be impossible to observe them, even with the most powerful compound microscopes, since protein molecules would be below the limits of resolution of these instruments. Geneticists became resigned to investigating their invisible genes, just as chemists study their invisible molecules and the physicists their invisible sub-atomic particles by indirect means.

To be sure some rather sophisticated methods for tagging chromosomes had developed for *Drosophila*, *Zea mays*, and a few other species. Stern had made homologous chromosomes different in *Drosophila* as Creighton and McClintock had done for corn. Dobzhansky had used radiations to break chromosomes in order to make a crude-genetic map of the second chromosome (1930) and to demonstrate translocations (1929), both in *Drosophila*. None of these methods, however, had the precision that was so highly desirable.

But more was needed than these gross changes. The *Drosophila* workers were postulating all sorts of chromosomal rearrangements to explain aberrations in their genetic results. As noted earlier, cases of reduced or eliminated crossing-over were blamed on inversions. The *bar eye* allele was suspected to be a duplication of one of the loci responsible for normal eyes. Other aberrant genetic results were assumed to be consequences of the translocation of gene loci from one chromosome to another.

These explanations for chromosomal rearrangements were brilliant hypotheses to solve difficult problems yet, except in the case of large translocations, they could not be confirmed by cytological means. This lack of confirmation made the claims of geneticists "just too much" for some biologists. Was the *Drosophila* group erecting a reliable edifice of science or were they constructing a house of cards? The answer depended on whom you asked.

And for nearly half a century a splendid method for answering these questions had been available but its usefulness not apparent. In 1881 Balbiani had described the strange structure of the nuclei in salivary glands and Malpighian tubules in larvae of the fly *Chironomus*. The chromosomes were visible in non-dividing cells. They were very large and appeared to be fused as a continuous spireme all twisted and jumbled together in the nucleus. They were cross banded. Thereafter similar descriptions were published for other Diptera (Painter, 1934*a*).

In contrast with Mendel's paper, Balbiani's was well known. E. B. Wilson (1900, p. 36) wrote:

> The most striking case of this kind [the chromatin of resting nucleus forming a continuous spireme] occurs in the salivary glands of dipterous larvae (*Chironomus*) where, as described by Balbiani, the chromatin has the form of a single convoluted thread, composed of transverse discs and terminating at each end in a large nucleolus.

Balbiani's figure was reproduced by Wilson. The discs were also called chromo-

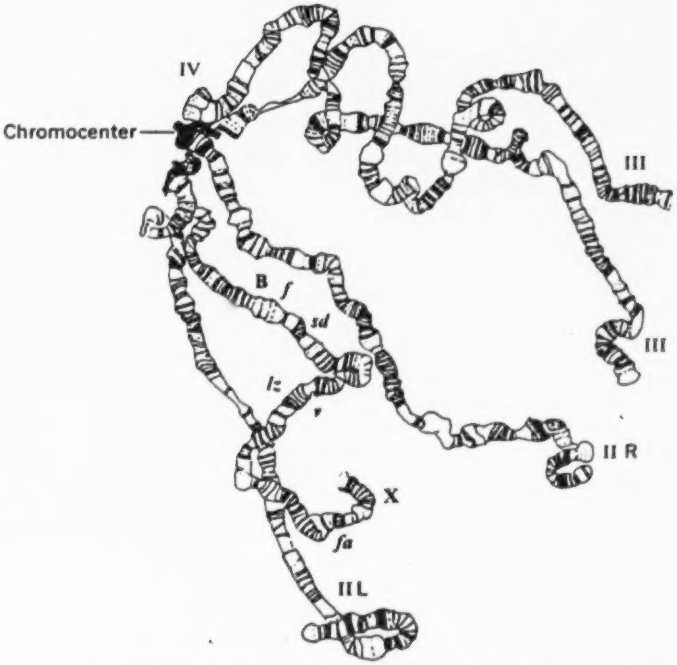

FIG. 45. Painter's first illustration of the salivary gland chromosomes of *Drosophila melanogaster*. The chromosomes are attached to the chromocenter, the **X** and the fourth by their ends. The two large autosomes are attached by their middles and, hence, have two arms (labelled L and R for left and right, in terms of the linkage maps). The letters show the provisional locations of some of the genes. (Painter, 1934*b*)

meres and were thought to divide in prophase (Sharp, 1934, p. 141, who also reproduces Balbiani's figure).

The possible importance of these banded chromosomes may have been missed because they were thought to be part of a continuous spireme and not individual chromosomes.

In 1933 Heitz and Bauer studied these giant banded chromosomes in another dipteran, *Bibio*, and reported that the chromosomes were not in a continuous spireme but consisted of the haploid number of elements. They therefore concluded that each salivary gland chromosome consisted of the two homologues fused together. When the cells were squashed chromosomes were spread out and could be studied. Of the greatest importance was their report that the banding pattern appeared to be specific for the regions of the chromosomes. That meant that the individual chromosomes could be identified by their characteristic banding pattern.

Later that same year Painter (1933) published a preliminary paper describing the similar huge salivary gland chromosomes of *Drosophila melanogaster*. They were at least 100 times as long as metaphase chromosomes. The homologous chromosomes were fused and the line of separation was difficult to see.

Once again, we have a case of simultaneous and independent discovery, for Painter (1934*a*) wrote,

> As I was in the midst of my first year's work, an article appeared by Heitz and Baur [=Bauer] dealing with the salivary chromosomes of *Bibio hortulanus*.

Painter had discovered the salivary gland chromosomes for himself; he was not aware of the extensive literature on the subject (1934*b*) until after his work was well under way.

Painter followed his first report with a series of papers describing in great detail the structure of the four pairs of homologous chromosomes (1934*a*, 1934*b*, 1934*c*, 1935) and determined which salivary gland chromosome corresponded with the four linkage groups (Fig. 45). Figure 46 is a photograph of some of the chromosomes of *Drosophila pseudoobscura* and *Drosophila persimilis.*

Your students may wish to speculate on how Painter was able to associate specific linkage groups with those cytological zebras of Figures 45 and 46. Some may suggest that if a specific inversion, for example the **C** inversion used in Muller's **ClB** stock, is known from the genetic data to be on the **X**, then the salivary gland chromosome that has an inverted section of bands would probably be the **X**. In the case of the **ClB** individuals, one of the **X** chromosomes would have one sequence of bands and the other would have a reversed sequence, since only heterozygous individuals are viable. Confirmation would come when other inversions ("crossover suppressors") of known linkage groups could be associated with the specific salivary gland chromosomes.

Painter was even able to determine the approximate position of gene loci.

> There are three general ways of determining the position of gene loci. Simple mutual translocations or inversions in which we know genetically between what genes the break or breaks have occurred; short deletions where we know what genes are missing; and a study of a series of breaks all falling between the same two gene loci.

Figure 45 shows the location of a few **X** chromosome genes.

This method was pure gold and many geneticists realized it at once. Th. Dobzhanksy told me this story long ago. Painter's first paper was reported at a seminar at Cal Tech and immediately thereafter Bridges came rushing into Dobzhansky's lab and said "Dobzhansky where are the salivary glands?" Bridges started work immediately and prepared maps of the *melanogaster* salivary gland chromosomes (1935, 1938, and 1939 with his son P. N. Bridges). Dobzhansky himself was to use the salivary gland chromosomes of *Drosophila pseudoobscura* (Fig. 46) and other wild species to obtain the basic data for his classic series *Genetics of Natural Populations* (reprinted in Lewontin, Moore, Provine, and Wallace, 1981). The salivary gland chromosomes attracted considerable attention. See, for example, Koltzoff (1934), Muller (1935), and Ris and Crouse (1945).

The bands on the salivary glands provided a critical cytological test for the many deductions the *Drosophila* workers had made on the basis of genetic data alone. Where they had invoked a reversed order of the genes to explain the absence of crossing-over, the bands on the salivary gland chromosomes were reversed. When their data suggested that a portion of one chromosome had become attached to another, the bands were found to be translocated. From some strange data they deduced that a small portion of a chromosome must have disappeared. The salivary gland chromosomes then revealed a few missing bands. The *bar eye* allele was suspected to be caused by the duplication of a small portion of the **X** chromosome. Figure 47 shows this to be true.

The *Drosophila* group had the last laugh—they had demanded a seemingly endless list of chromosomal aberrations if they were to explain their genetic data and the bands on the salivary gland chromosomes confirmed their hypotheses.

WHERE ARE THE GENES?

Now that specific and minute portions of *Drosophila* chromosomes could be defined, there was great interest in discovering, if possible, the place occupied by the genes. Were the bands the genes? Was the non-staining area between the bands genetically inert?

Attempts to localize the positions of genes were based mainly on studies of small deletions. These could be produced in large numbers with X-rays. It was not possible,

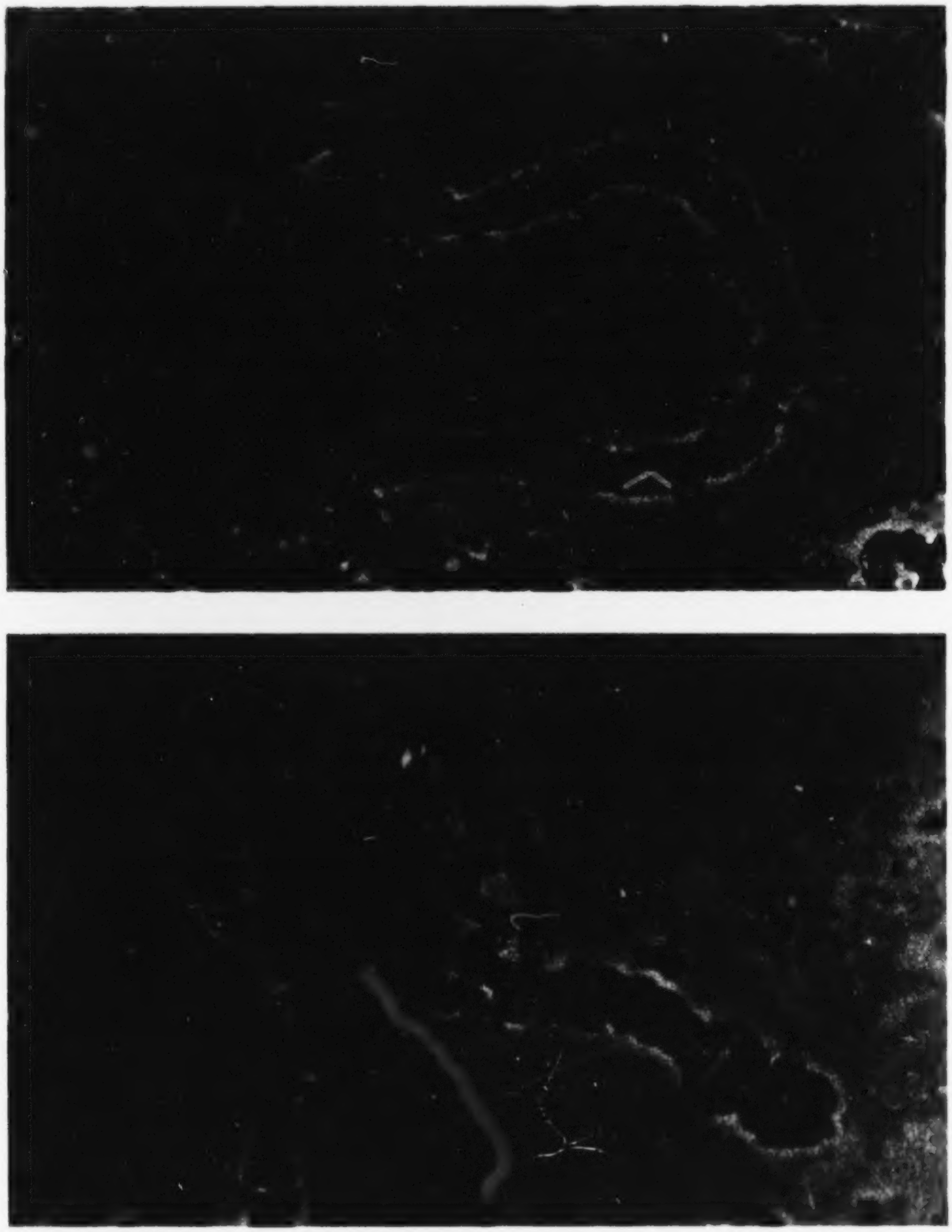

Fig. 46. Photographs of salivary gland chromosomes. The upper one is the so-called Klamath gene arrangement in *Drosophila persimilis.* The lower figure shows the area of the inversion of an individual heterozygous for the Pikes Peak and Standard gene arrangements in *Drosophila pseudoobscura.* The chromosomes at the bottom left are fused but slightly above the inversion begins—it can be seen that the bands do not correspond and pairing is not possible. One of the inverted sections makes a twist and can pair, as in the topmost section. Farther on the two homologues are separate but at the bottom right their loci are the same and pairing is possible again. (Photographs by Betty C. Moore)

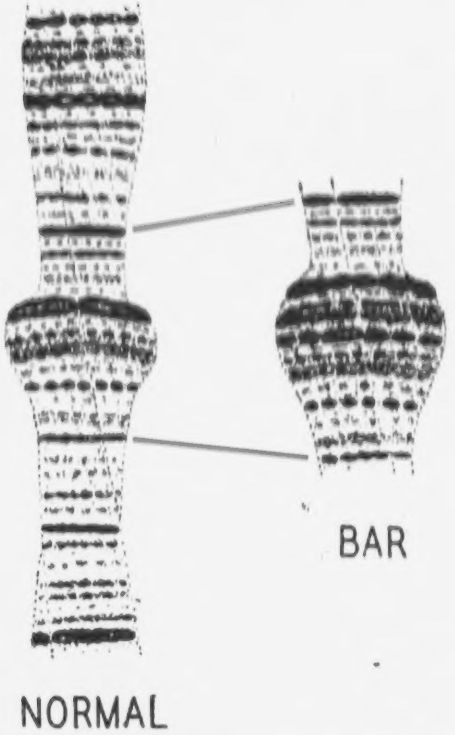

FIG. 47. Salivary gland chromosomes showing the area of *bar* in the **X** chromosome. The lines show the corresponding bands on the two chromosomes. (Bridges, *Science* 83:210, 1936)

of course, to induce deletions at specific places in chromosomes so the procedure was to irradiate many flies and examine their offspring in the hope of obtaining deletions in the desired region of the chromosome. A very large amount of work was required but for a motivated and dedicated geneticist it was worth it.

The following example is from the work of Demerec and Hoover (1936). They studied stocks with three deficiencies near one end of the **X** chromosome. Most deficiencies, except when very small, are lethal when homozygous but they can be carried in the heterozygous state.

Deficiencies have a special genetic effect as will be seen from the following consideration. Assume that a fly is heterozygous for a deficiency that includes the locus of gene **A**. That means that the allele at the **A** locus on the normal chromosome will determine the phenotype, since there is nothing on the chromosome with the deficiency to counteract its effect. This situation is similar to that in *Drosophila* males where, with the **Y** having almost no genes, whatever is on the **X** will determine the phenotype.

Demerec and Hoover determined the precise bands that were absent in the three deletions. They selected three mutant alleles, **y** (*yellow*—a body color mutant), **ac** (*achaete*—removes some bristles), and **sc** (*scute*—removes other bristles), which previous study had shown to be almost at the end of the chromosome.

The crosses were made in such a way that the flies studied would have one entire chromosome with **y**, **ac**, and **sc** and the other with one of the deficiencies but no mutant alleles. The experiments are diagrammed in Figure 48.

The first deficiency removed the 4 bands at the tip of the chromosome. The flies were *wild-type* indicating that the loci of the genes being used were not in the first 4 bands. The next deficiency removed the 8 terminal bands. The flies were *yellow* and *achaete*, showing that the loci for those alleles were in the terminal 8 bands. However, the first deficiency showed they were not in the first 4 bands. Therefore the *yellow* locus and the *achaete* locus must be in the regions of bands 4–8. The third deficiency removed the terminal 10 bands and this time the flies were *yellow*, *achaete*, and *scute*. Therefore, the locus for *scute* must be in the region covered by bands 8–10.

Using this method *Drosophila* workers were able to determine the approximate loci for many genes. No locus was found in the interband regions and, in a few cases, it was possible to place a locus in a small region having a single band. These observations suggested the tentative hypothesis that the bands or some portion of them are the gene loci.

If this hypothesis is true, a tentative estimate for the number of genes in *Drosophila melanogaster* could be obtained by counting the bands. This is a tricky business because the number of bands depends to some

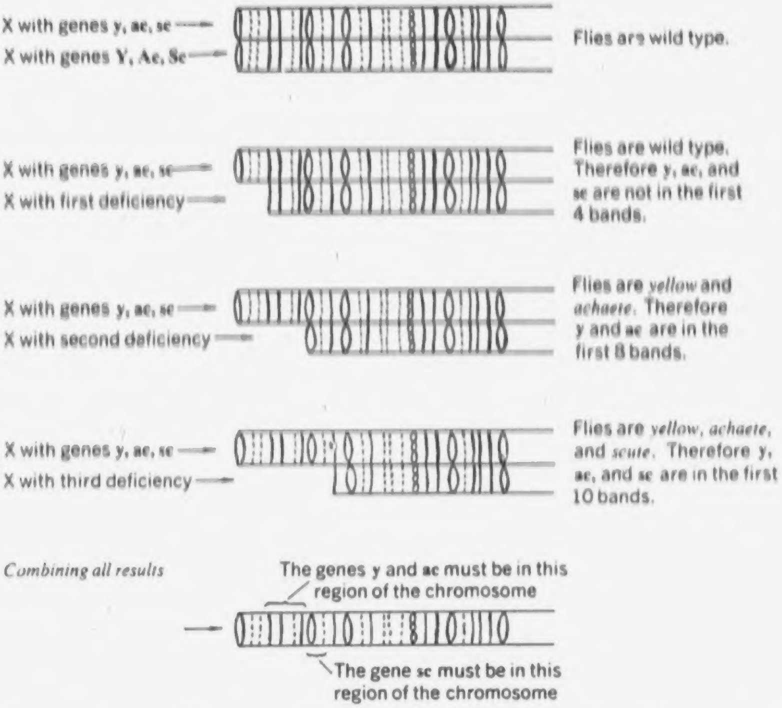
X with genes y, ac, sc
X with genes Y, Ac, Sc
Flies are wild type.
X with genes y, ac, sc
X with first deficiency
Flies are wild type. Therefore y, ac, and sc are not in the first 4 bands.
X with genes y, ac, sc
X with second deficiency
Flies are *yellow* and *achaete*. Therefore y and ac are in the first 8 bands.
X with genes y, ac, sc
X with third deficiency
Flies are *yellow*, *achaete*, and *scute*. Therefore y, ac, and sc are in the first 10 bands.
Combining all results
The genes y and ac must be in this region of the chromosome
The gene sc must be in this region of the chromosome

FIG. 48. The experiments of Demerec and Hoover to localize the genes of the **X** chromosome. See text for details.

extent on how the chromosomes are stained—they vary from bands that stain heavily to others so indistinct as to be at the limit of resolution. Nevertheless, there seemed to be about 5,000 bands so that was taken as the tentative minimum number of genes.

Once the genes were located on the salivary gland chromosomes, a comparison of the chromosomal maps could be made with the genetic maps. Bridges made an especially careful study and his comparison is shown in Figure 49. The resemblance is close. Although this is what geneticists expected, still it was astonishing. The comparison is being made here between one set of data based on the phenotypes of offspring of genetic crosses and another set of data based on the cytological descriptions. The two sets of data are about as different as one can imagine. And, once again, it was Calvin Bridges who did so much to validate the hypothesis.

The genetic data support the hypothesis that the genes are arranged in linear order and in a certain sequence. The cytological data support the same hypothesis. Once again, genetics and cytology were found to be mutually supportive and that fact in itself proved the hypothesis as true beyond all reasonable doubt.

This ability to check the findings in one field with findings in a completely different field is one of the most powerful techniques available to scientists. Two sorts of genetic data or two sorts of cytological data supporting the hypothesis of the linear order of genes are not as convincing as one set of genetic data in concordance with one set of cytological data.

The Suttonian paradigm, having guided the most gifted cytologists and geneticists for three decades, was now losing its ability to suggest new and exciting research problems. This was not because it was wrong but because it was so right. Its well-estab-

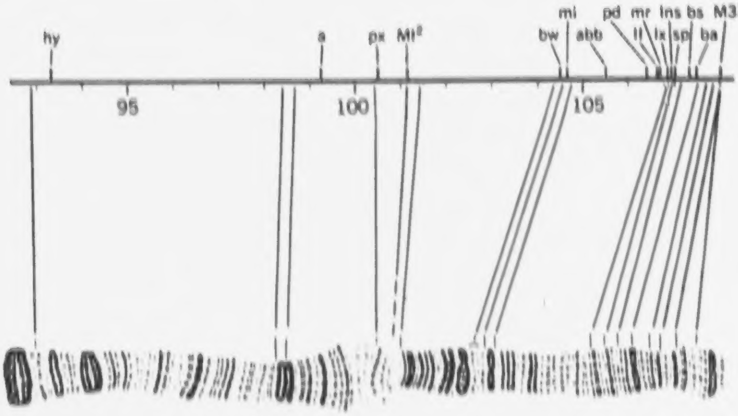

FIG. 49. Corresponding points in the salivary chromosome and the linkage map for the tip of the second chromosome of *Drosophila melanogaster*. (Modified from Bridges, 1937)

lished principles were found to be of great importance in experimental medicine and experimental agriculture. The experimental and theoretical challenges lay elsewhere and, after a summing-up and a pedagogical diversion, we shall see what they were.

THE CONCEPTUAL FOUNDATION OF CLASSICAL GENETICS

After thousands of crosses had been made and millions of offspring classified, geneticists of the late 1930s had the satisfying feeling that the big questions that had been asked for centuries had acceptable answers. When genetically unknown species were studied for the first time the rules of Mendel, Sutton, and Morgan accounted for the data.

The science of genetics had reached an acceptable level of maturity—it could predict the outcome of experiments. Genetics was the first branch of biology to reach this level of conceptual adequacy. It was inevitable that this be so. Even though it deals with the most basic problems of biology, it is the least complex part of biological science. The genotype must be simpler than the phenotype, since what is basic is less complex than what is derived. The genetic code is essentially universal in the realm of life, while the structure and functions of organisms take their myriad forms.

If one asks what had been accomplished in genetics and cytology the answer is that it was nothing less than discovering the rules governing the transmission of genes from parent to offspring. These rules, seemingly universal, held for plants, animals, and microorganisms. What are they?

Now follows a list of the major concepts of classical, or transmission, genetics.

1. The basic morphology, physiology, and molecular biology of an individual are determined by its inheritance, acting in a defined environment.

2. Although an individual's material inheritance is small in quantity, it contains all the genetic information in its genes necessary for the development of an organism like its parents.

3. Genes are parts of chromosomes. (Later research was to show that some genetic information is contained in mitochondria, plastids, viruses, and some virus-like bodies.)

4. Each gene usually occupies a definite site, its locus, in the chromosome. Understandable exceptions to this concept—inversions and translocations—were known and examples of the movement of genetic material from chromosome to chromosome have increased with time.

5. Each chromosome has many genes, except for a few cases like the Y of *Dro-*

sophila, and the genes are arranged in a linear order.

6. The somatic cells contain two of each kind of chromosome, that is, they are in homologous pairs. That means that every gene locus is represented twice. There are some well-known exceptions. In some species, bees for example, queens and workers are diploid females and the drones are monoploid males. Sex chromosomes are another exception where **XO** and **XY** males have only single copies of sex-linked genes. Also some of the cells in some tissues of some animals may be polyploid, as in our livers.

7. During each mitotic cycle the genes are duplicated from the chemical substances in the cell. Cellular duplication involves a prior genic duplication.

8. Although genes are characterized by great stability through time, possibly replicating a million times in many generations before any heritable change, a mutation, occur. Thus genes are capable of existing in several states known as alleles.

9. Genes can be transferred from one homologous chromosome to another by cytological crossing-over. This is a normal part of meiosis but there are a few exceptions, such as the male of *Drosophila melanogaster*, where crossing-over does not occur in genetically active regions.

10. The meiotic process ensures that each gamete receives one chromosome of each homologous pair. *Which* of the two homologues it receives is a matter of chance. Thus the gametes will receive one or the other of each gene pair (segregation). Each homologue, with the genes it contains, will be distributed to half of the gametes. **XO** males are an obvious exception.

11. In the formation of gametes, the segregation of the chromosomes of one homologous pair, with the genes it contains, has no effect on the segregation of the other pairs of homologous chromosomes with their genes.

12. Fertilization consists of the random union of ova and sperm, each with one chromosome of every homologous pair. Therefore, the zygote receives one chromosome of each homologous pair from the mother and one from the father. Again, sex chromosomes introduce an understandable exception.

13. When two different alleles of the same locus are present, the individual is heterozygous for that gene. The allele with the greater phenotypic effect is known as the dominant, and the other as the recessive. In most cases the heterozygote appears to be identical with individuals homozygous for the dominant allele. Less frequently the heterozygotes are intermediate.

14. Finally, genes must produce their effects through the production of chemical substances, which in turn control the biochemical reactions of the cell. In the 1930s this was little more than a tentative hypothesis but no other alternative seemed possible. Some geneticists suggested that the major function of genes is to produce specific enzymes, which in turn control the life of the cell.

These 14 propositions account for most of the phenomena of classical, or transmission, genetics. They formed a satisfying conceptual whole. But this was not enough. The inquisitive human mind is more stimulated by what is unknown than by what is known. One knew with great precision how the genes for eye color were inherited but essentially nothing of the structure of those genes or their mode of action. One could sense that would be the concern of the next major paradigm of genetics—carrying the analysis to the level of cells and molecules.

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References more of historical interest. G. E. Allen (1966*a*, 1966*b*, 1969, 1974*a*, 1974*b*, 1975*a*, 1975*b*, *1978, 1979, 1983, 1985), Blakeslee (1936), Carlson (*1981), Cook (1937), Crew (1966), Dunn (*1951, *1965*a*, 1965*b*), Gilbert (1978), Glass (1963), Haldane (1938), Hall (1969), Hayes and Burnham (1959), Komai (1967), Mayr (*1982), Moore (1983), Morgan (1926*b*, 1939, 1940, 1941, 1942), Muller (1943), Payne (n.d.), Robinson (1979), Shine and Wrobel (1976), Stern (1970), and Sturtevant (1959, 1965*a*).

GENETIC PROBLEMS INVOLVING *DROSOPHILA*

If students are asked to solve genetic problems using *Drosophila*, they will come to realize very quickly what they understand and do not understand about genetics. *Drosophila* can be used for the more basic crosses of the monohybrid and dihybrid variety similar to those suggested earlier. Here are a few examples and the standard textbooks of genetics will have many more.

In *Drosophila vestigial-wings* (**v**) is an autosomal recessive to the wild-type *long-wings* (**V**). *Sepia-eye* color (**s**) is an autosomal recessive to the wild-type *red-eye* (**S**).

1. Describe the genotype and phenotype of the F_1 and F_2 of a cross of a *vestigial* female and a *sepia* male.

2. Describe the genotype and phenotype of the F_1 and F_2 of a cross of a *vestigial* male and a *sepia* female.

3. A normal-appearing male fly, of unknown genotype, is crossed with a female homozygous for both *sepia* and *vestigial*. The offspring were: ¼ *sepia-vestigial*, ¼ *red-vestigial*, ¼ *sepia-long*, and ¼ *red-long*. What was the genotype and phenotype of the male parent?

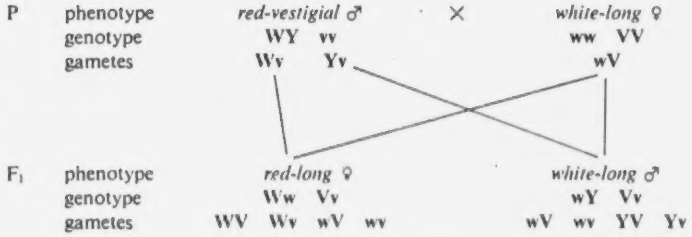
Problems of the sort given in 3 are especially valuable. If students have difficulties solving them the following hint should help. First, the problem should be solved for one pair of alleles at a time. A cross involving dominant and recessive autosomal alleles can have four possible outcomes. All of the offspring could have the phenotype of the recessive, which would mean that both parents had the recessive genotype. Or the offspring could all be of the dominant phenotype, which would mean that one parent must have been homozygous for the dominant phenotype and the other parent could have been either homozygous for the dominant or recessive allele or heterozygous. The third possibility would be a 3:1 ratio, indicating that both parents were heterozygotes. And finally, there could be a 1:1 ratio, meaning that one parent was a homozygous recessive and the other a heterozygote. One cannot tell, in the case of autosomal genes, which parent is which.

In problem 3, half are *sepia* and half are *red*. Therefore, one parent must have been **Ss** and the other **ss**. Since we know that the female parent was **ss**, the male must have been **Ss**. In addition, half of the offspring are *vestigial* and half are *long*. So one of the parents, the female, must have been **vv** and so the male parent must have been **Vv**.

4. In an F_1 the following offspring were obtained: ⅜ *red-long*, ⅜ *red-vestigial*, ⅛ *sepia-long*, and ⅛ *sepia-vestigial*. What were the genotypes and phenotypes of the parents?

5. A female with *sepia-eyes* and *long-wings* is crossed with a male of unknown parentage. The offspring were: ¾ *red-long* and ¼ *red-vestigial*. What was the genotype of the male?

Crosses involving autosomal and sex-linked genes represent a somewhat higher level of difficulty. The following cross is an example.



SPERM

OVA

	wV	wv	YV	Yv
WV	Ww VV *red-long* ♀	Ww Vv *red-long* ♀	WY VV *red-long* ♂	WY Vv *red-long* ♂
Wv	Ww Vv *red-long* ♀	Ww vv *red-vestigial* ♀	WY Vv *red-long* ♂	WY vv *red-vestigial* ♂
wV	ww VV *white-long* ♀	ww Vv *white-long* ♀	wY VV *white-long* ♂	wY Vv *white-long* ♂
wv	ww Vv *white-long* ♀	ww vv *white-vestigial* ♀	wY Vv *white-long* ♂	wY vv *white-vestigial* ♂

FIG. 50. Diagram of a cross involving an autosomal and a sex-linked gene.

White-eyes is a sex-linked recessive to the wild-type *red-eyes.* The mutant *vestigial-wing* is an autosomal recessive to the wild-type *long-wing.* Figure 50 diagrams a cross of a *red-vestigial* male with a *white-long* female. The F_2 ratios, which can be derived from the genetic checkerboard, will be new to your students. They are:

Females: 3/8 *red-long,* 3/8 *white-long,* 1/8 *red-vestigial,* 1/8 *white-vestigial.*
Males: the same.

If this seems confusing to your students, have them determine the genotypes and phenotypes for the sex-linked alleles and the autosomal alleles separately. Ask them why the F_2 does not show the usual 9:3:3:1 ratio, since the two pairs of alleles are on different chromosomes and should we not expect independent assortment? Some students may realize that the problem here is that the **Y** chromosome does not have the eye color locus. Therefore, instead of the P generation having a total of 4 alleles in the two parents, there are only 3. If the **Y** had an active locus there would have been a total of 4 alleles, and the F_2 ratio would have been 9:3:3:1.

Then have the students do the reverse cross, *white-long* male × *red-vestigial* female, to see if the results are the same.

Once the students have mastered problems of this sort, it will be challenging for them to start with the offspring and see what can be said about the parents. Here are some examples.

6. The following offspring were observed in an F_1:

Males: ½ *white-vestigial*, ½ *white-long*.
Females: ½ *red-vestigial*, ½ *red-long*.

What are the genotypes and phenotypes of the parents?

This type of problem should be solved for the autosomal alleles first using the method described in problem 3. Then the inheritance of the sex chromosome alleles should be solved, remembering the following relations:

a. The daughters receive one **X** from the father and one from the mother (see Fig. 39 for a reminder).

b. The sons receive their **X** chromosome only from the mother. Therefore, the phenotypes of the males will indicate what the genotype of the mother must have been. Using the *white-eyes* and *red-eyes* alleles as an example, if all the sons have *red-eyes*, the mother must have been homozygous for *red-eyes*, **WW**. If all of the sons have *white-eyes*, the mother must have been homozygous for *white-eyes* **ww**. And lastly, if half of the sons have *white-eyes* and half have *red-eyes*, the mother must have had both alleles and have been a *red-eyed* heterozygous, **Ww**.

One can tell a good deal, but not all, about the parents in problem 6. The phenotype of the autosomal alleles shows a 1:1 ratio, which means one of the parents was **Vv** and the other **vv**. There is no way of telling which is which for autosomal genes.

All of the males have *white-eyes*, so the mother must have been **ww**. Now we have to determine what the eye color of the father must have been. Since we have established that the mother was homozygous for *white-eyes*, all of her daughters would have received an **X** from her with **w**. Yet we are told that all of her daughters are *red-eyed*. Therefore, the daughters' other **X**, which comes from the father, must have carried the allele for red, **W**. We conclude that the father was **WY**.

Therefore the cross was either **wwvv** female × **WYVv** male or **wwVv** female × **WYvv** male.

Here are some additional problems involving the same genes.

7. These offspring were obtained:

Males: ¼ *white-long*, ¼ *white-vestigial*, ¼ *red-long*, ¼ *red-vestigial*.
Females: ½ *red-long*, ½ *red-vestigial*.

What were the genotypes and phenotypes of the parents?

8. These were the F_1 of another cross:

Males: ⅜ *white-long*, ⅜ *red-long*, ⅛ *white-vestigial*, ⅛ *red-vestigial*. .
Females: ⅜ *white-long*, ⅜ *red-long*, ⅛ *white-vestigial*, ⅛ *red-vestigial*.

What were the genotypes and phenotypes of the parents?

9. In still another cross these were the F_1:

Males: ⅜ *white-long*, ⅜ *red-long*, ⅛ *white-vestigial*, ⅛ *red-vestigial*.
Females: ¾ *red-long*, ¼ *red-vestigial*.

What were the genotypes and phenotypes of the parents?

A final type of problem will involve linked genes and, hence, crossing-over. This may appeal to the more interested students.

In *Drosophila black-body* color (**b**) is recessive to *gray-body* (**B**). The locus is on the same chromosome as the *vestigial-wing* (**v**) and *long-wing* (**V**) used in the preceding problems. Bridges and Brehme (1944) place the locus of *black* at 48.5 and *vestigial* at 67, both on Chromosome 2. The difference, 16.5 units, means that crossing-over occurs in that percentage of the cases.

These crossover values, which are the basis of the genetic map, are determined experimentally. Therefore, students cannot determine the percentages of genotypes and phenotypes in the F_1 and F_2 without being told the crossover percentages.

10. Describe the F_1 and F_2 of a cross of a *black-vestigial* female and a *gray-long* male. For simplicity we will assume that the two loci are 17 units apart in the same chromosome.

Figure 51 develops the answer, line by

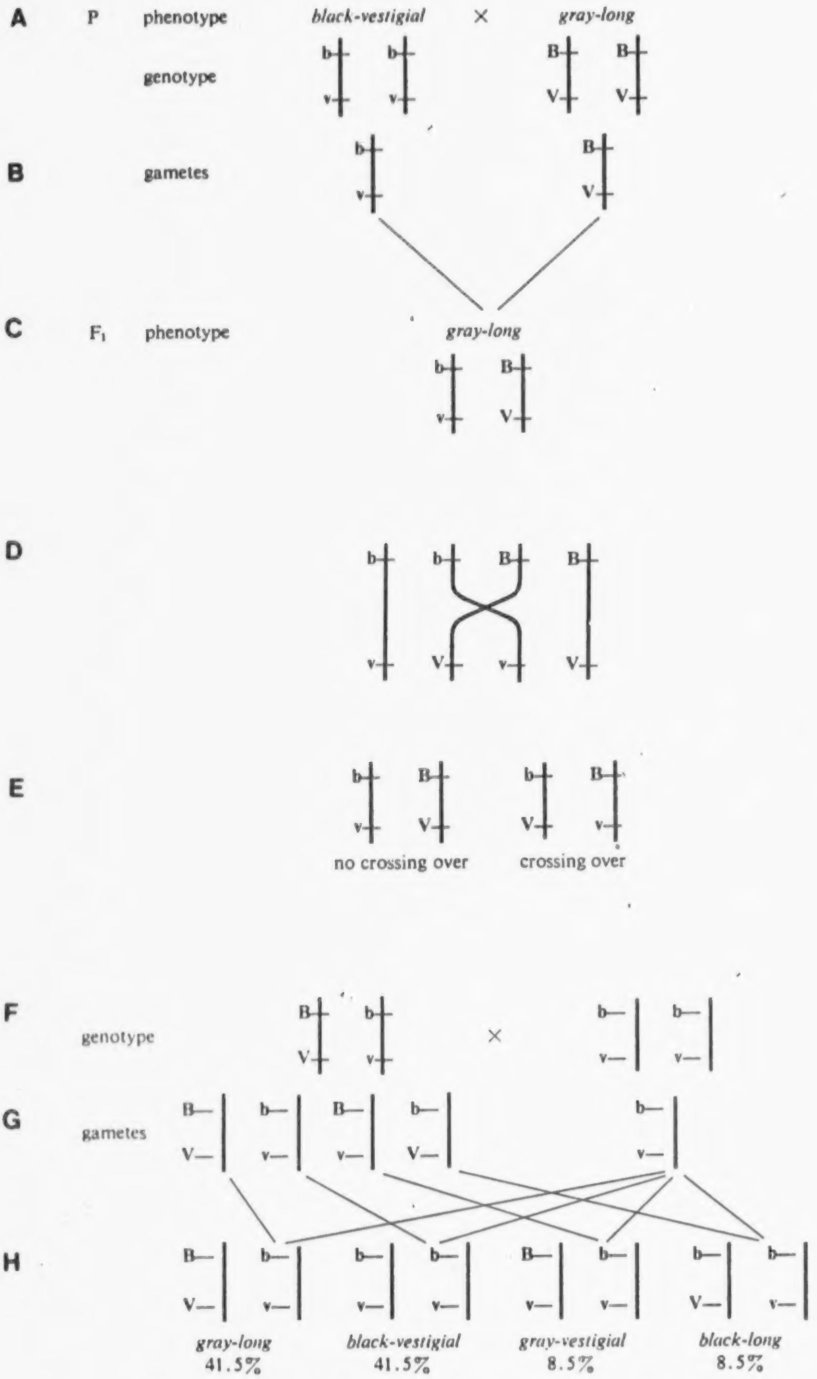


FIG. 51. Diagram of a cross involving two linked genes.

051 157

line. Line A shows the phenotype and genotype of the parents. The vertical line connecting the alleles represents a chromosome.

Line B shows the gametes produced by each parent. There is no crossing-over in the male so his sperm will be **BV**. There is crossing-over in females but since the two chromosomes are identical for the loci being followed, it will not be detected.

Line C shows the F_1 individuals—all of the same genotype and phenotype. In order to measure the amount of crossing-over, we use F_1 *females* only for further study.

Line D shows what will happen during meiosis in the F_1 female. Crossing-over occurs after the homologous chromosomes have synapsed and replicated to form 4 chromatids. The mechanics of crossing-over are such that, at any one locus, only 2 of the 4 strands will cross-over. This means that there will be 2 chromatids that do not cross-over at this locus and 2 that do. The products are shown in E. It should be obvious to your students that the chromatids resulting from crossing-over will be in equal numbers. In addition the 2 non-crossover chromatids will also be in equal numbers.

Since we know that crossing-over accounts for 17 percent of the chromatids, 8.5 percent will be **bV** and 8.5 percent will be **Bv**. The 83 percent of the non-crossover chromatids will be divided equally between **bv** and **BV**—41.5 percent of each.

In line F we take one of the F_1 females (from line C) and do a test-cross, that is, cross her with a male homozygous for both pairs of recessive alleles. In experiments involving crossing-over the female being tested is always crossed with a male homozygous for all recessive alleles. Should any of your students be flagellants, they could try to solve a variant of problem 10 by crossing two F_1 individuals to obtain an F_2.

Line G shows the gametes of the female, as we derived them in lines D and E, and the single class of sperm of the male.

Ova and sperm combine at random and the percentages of the genotypes and phenotypes of the F_2 are shown in line H.

11. In *Drosophila, ebony* (**e**) and *stripe* (**s**) are autosomal recessive genes and are parts of the same chromosome. *Ebony* makes the color of the body a shiny black. *Stripe* produces a dark line on the thorax. There is 8 percent crossing-over between them. Describe the offspring of a female heterozygous for both genes (her father was *ebony-stripe*) with an *ebony-stripe* male.

Problems of this sort are simple to make up—check any standard genetics textbook for genetic maps showing crossover distances between loci.

THE CHANGING PARADIGM

By the end of the 1930s there were no big questions remaining in transmission genetics so the emphasis switched to the difficult questions of "What do genes do?" and "What is the chemical nature of genes?" Of course there had been interest in these questions from the turn of the century but, with the techniques available, there was little possibility of obtaining any detailed answers. None of the routine technology of today such as electron microscopes, radioactive isotopes, computers, chromatography, and unbelievably sophisticated analytical instruments was available. There was no NSF, no overhead, and little external source of support for research. Laboratory assistants and post-docs were scarce. Teaching and research were accepted as of equal importance in the operations of the great universities so less time was available for research. E. B. Wilson was able to accomplish incredible research and scientific publication while carrying a teaching load that would astonish most cutting-edge biologists today.

Then, too, the fields concerned with gene structure and function—cell biology and biochemistry—had not advanced to the stage where such questions could be answered in a definitive manner.

But one ingredient for scientific discovery, in fact the *sine qua non,* was not lacking. That was brains. By the time more sophisticated techniques became available, students of the gene had established in a general way that genes control the metabolic activities of cells and that the hereditary material was probably nucleic acid. The stage was set for Watson and Crick to formalize in 1953 the next paradigm of genetics—which shortly became the central paradigm of the biological sciences.

WHAT DO GENES DO?

Nevertheless the crude probes available before 1953 made possible important discoveries in gene function. Among the probes were those developed for studying enzymes. During the first half of the 20th century one of the most vigorous fields of cell biology and biochemistry was the study of enzymes. Enzymes were viewed as one of the major factors making life possible. The sorts of reactions that were known or suspected to occur in cells simply could not take place without these organic catalysts.

In one of those strange episodes in the history of ideas, genes and enzymes were first linked at a time when very little was known about either.

An English physician, Archibald E. Garrod (1857–1936), had a patient, a baby, with a rare disease—alkaptonuria. It was so named because the urine of patients has alkapton bodies, which consist largely of homogentisic acid. That substance becomes dark red or black when oxidized. A clue to the patient's problem was stains on its diapers (or, since the baby was British, its nappys).

Garrod knew that the baby's parents were first cousins and he wondered if alkaptonuria might be an inherited disease. In 1902 (!) he consulted Bateson, who suggested that the disease might be due to recessive alleles.

Garrod (1908*a*, 1908*b*; Harris, 1963) spoke of alkaptonuria and similar ailments as "inborn errors of metabolism." Bateson continued to be interested and wrote in 1913*a* (p. 233):

> Alkaptonuria must be regarded as due to the absence of a certain ferment which has the power of decomposing the substance alkapton. In a normal body that substance is not present in the urine, because it has been broken up by the responsible ferment; but when the organism is deficient in the power to produce that ferment, then the alkapton is excreted undecomposed and the urine is coloured by it.

The hypothesis, then, is "one allelomorph, one ferment." Thirty years later, with the terminology brought up to date, this was to become one of the most important hypotheses guiding genetic research.

Neither Garrod nor alkaptonuria is mentioned in any of the books written by the Morgan school in the years of active discovery. Even if Morgan knew of Garrod's hypothesis he may have ignored it. Morgan was so pro,experimental science and anti all else—including non-experimental science—that he would have viewed Garrod's hypothesis as useless, for he had written:

> It is the perogative of science, in comparison with the speculative procedures of philosophy and metaphysics, to cherish those theories that can be given an experimental verification and to disregard the rest, not because they are wrong, but because they are useless.

Sturtevant in his history (1965*a*, p. 134) notes,

> There are other examples of a widespread failure to appreciate first-rate discoveries in genetics, and it is perhaps worthwhile to examine some of these briefly. Perhaps the most remarkable examples are the work of . . . and of Garrod on biochemical genetics . . . .
>
> Garrod was concerned with biochemical processes, and few geneticists were well enough grounded in biochemistry to be willing to make the moderate effort required to understand what he was talking about.

But possibly an important part of the answer lies elsewhere. When research programs were developing rapidly and productively, as they were for the *Drosophila* workers, there is little stimulus to look for new things to do. It was not until the 1930s, with transmission genetics satisfactorily explained, that geneticists began an intensive study of the sorts of problems that interested Garrod.

METABOLIC PATHWAYS IN CELLS

George W. Beadle (born 1903), Edward L. Tatum (1909–1975), and Boris Ephrussi (1901–1979) were leaders in the quest for information on how genes act. By the late

1930s there was considerable information about cell metabolism. That fundamental reaction of all life,

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$$

had been resolved into several dozen separate reactions, each controlled by a specific enzyme.

The elucidation of this one metabolic pathway had required the efforts of many scientists for many years. One of the major problems was the speed of the reactions, often requiring a fraction of a second. How was one to study a reaction that would be over before the investigator knew it had started? The standard way was to use chemical substances ("enzyme poisons") that would block the action of a specific enzyme. The result would be that the substrate for that enzyme would then accumulate in the cell and could possibly be detected and identified.

Assume, for example, that one metabolic pathway in cells involves molecule A being changed into molecule B and then B into molecule C and then down the alphabet to molecule Z. We will assume that the change from A to B is controlled by enzyme A-ase and from B to C by B-ase and from Y to Z by Y-ase. All we know at first is that the cell changes molecule A to molecule Z. That is, the conversion may be accomplished by a single enzyme in a single reaction.

One of the first enzyme poisons we try is cyanide. We observe that no Z is formed and, instead, a previously undetected molecule, M, is found. What can we conclude? Can we say that the cell converts A to Z in two steps: A is converted to M and then M to Z? That may have been said a few generations earlier but, as the complexity of intracellular metabolism came to be understood in the 1930s, the conclusion would be no more than "there are at least two intermediary steps from A to Z."

Other poisons could be tried, and with time more and more could be learned about normal metabolism by throwing these chemical wrenches into the biochemical gears of the cell.

Some early studies of Beadle and Ephrussi on the way that eye color genes of *Drosophila* produce their effects had indicated that gene action might be mediated by enzymes. Enough was discovered to suggest that the hypothesis "one gene, one enzyme" might be a fruitful approach. The biochemistry of *Drosophila* proved to be too complex to test that hypothesis and for the first time that noble animal let a geneticist down.

So a long-standing experimental technique was invoked: if the experiment cannot be done with one organism, search for another one that is suitable. By this time Beadle was at the California Institute of Technology with Morgan. Before Morgan left Columbia, Bernard Dodge of the New York Botanical Garden gave him a culture of the red bread mold, *Neurospora crassa*, in the belief that it might be of use in genetic experiments. Morgan never used *Neurospora* but it was still being cultured in his laboratory when Beadle and Tatum sought an organism for their research.

NEUROSPORA CRASSA

Beadle and Tatum (1941) reasoned that lethal mutations change alleles so that they are incapable of producing an enzyme essential for the life of the organism. Thus they intended to induce lethal mutations with radiations and to study their biochemical effects. This might appear to your students to be a considerable problem since, if the lethal kills the individual, there would not appear to be much to investigate. But Beadle and Tatum solved that problem in what was surely one of the most innovative and productive lines of experimentation in the late 1930s and 1940s. Others must have thought so too because Beadle and Tatum shared a Nobel Prize for this work.

For reasons that will shortly become apparent they first had to determine exactly the minimum variety of molecules required for normal growth—the minimal medium. The menu was surprisingly simple: air, water, inorganic salts, sucrose, and the vitamin biotin. *Neurospora* is, of course, composed of innumerable organic compounds, all interacting as the life of that organism. Yet from those few raw materials it is able to synthesize all of the amino acids, proteins, fats, carbohydrates, nucleic acids, vitamins, and other substances of its body.

As an example of the many experiments done by Beadle and Tatum, we will discuss those concerned with the synthesis of the amino acid arginine. The working hypothesis was that specific genes control the production of specific enzymes that catalyze the reactions that lead to the formation of arginine. Presumably these genes could mutate to allelic forms that would either be unable to make the enzyme or not be able to make it in sufficient quantity. Since arginine is essential for the life of *Neurospora,* such mutations would be lethal.

Beadle and Tatum then devised a method for the production of these lethal mutations, for identifying them as related to the synthesis of arginine, and for maintaining them in culture in order to work out the metabolic pathway of arginine synthesis. This may sound impossible, especially when we realize that for most of its life cycle *Neurospora* is monoploid and hence any lethal mutations could not be carried as heterozygotes.

This was their game plan. First, X-rays were used to induce mutations. They assumed that all sorts of mutations would be produced, but by chance some might be involved with the production of arginine. When we remember how rare any specific mutation would be, the chance of obtaining the desired mutations would be exceedingly small.

Spores from the irradiated *Neurospora* were then placed on the minimal growth medium. Most of them grew, showing that whatever mutations may have occurred none was so serious as to prevent the *Neurospora* from synthesizing all of its substance from the few chemicals in the minimal medium. Other spores did not germinate, and among these might be some biochemical mutants that could not produce the enzymes necessary for normal growth and development. And somewhere among them might be genes involved in the synthesis of arginine. How could one find them? The spores were not germinating, so they were for practical purposes "dead."

The solution of this apparently insolvable difficulty was elegant in its simplicity and effectiveness. If the spores could not grow because they could not synthesize their own arginine, why not give it to them? And that is precisely what Beadle and Tatum did. Again most of the spores did not grow but a precious few did. Among these precious few might be mutants of genes involved in arginine synthesis.

The next, and critical, step in the analysis was to make sure that whatever was wrong with the spores was inherited. It could not be concluded that, just because the otherwise "lethal" spores could grow on arginine, that a mutational event was the cause.

The life cycle of *Neurospora* makes it ideal for some sorts of genetic analysis. The colonies are monoploid for nearly their entire life. There are two mating types, *A* and *a*, which cannot be distinguished except by their mating behavior. If colonies of *A* and *a* are grown together, parts of each will fuse and *A* nuclei will unite ("fertilize") with *a* nuclei to form diploid zygotes. Meiosis occurs immediately and 4 monoploid spores are formed. These divide, by mitosis, to produce 8 monoploid spores. These 8 spores are enclosed in an elongate spore sac (ascus). They are arranged in the sac in a linear order that reflects the two meiotic divisions and the single mitosis. The spore sacs can be opened under a microscope and the individual spores removed and placed in culture media. Thus one can obtain all of the products of meiosis of a single zygote.

The presumed mutant strains were crossed to normal strains. Meiosis occurred immediately afterwards and monoploid spores were formed. These were then isolated. Half were found to grow on the minimal medium and half only if arginine was added. These results were consistent with the hypothesis that the wild-type *Neurospora* had a gene **A**, which was necessary for the synthesis of arginine. The radiation treatment had caused a mutation of **A** to **a** and **a** was unable to play some essential role in arginine synthesis.

The experimental procedure appeared to be working and numerous genetic strains were isolated that required arginine for growth. Were all the genetic strains alike or had different genes mutated to alleles that could not synthesize arginine? Can your students suggest how one could go about answering that question?

There were two possible answers:

First, all of the mutant strains could be due to changes at a single gene locus.

Second, many different loci could have mutated. In this case one would suspect that many genes are involved in arginine synthesis: $\mathbf{A}_1$, $\mathbf{A}_2$, $\mathbf{A}_3$, $\mathbf{A}_x$, etc. Any one of these could have mutated to $\mathbf{a}_1$, $\mathbf{a}_2$, etc. In all these mutants the same phenotype would be observed—inability to grow on minimal medium without arginine.

Crosses could test the alternatives. If a single locus is involved, a cross of two strains would produce spores unable to grow without arginine. Alternatively, if different loci are involved, some of the spores will grow as wild-type colonies for the following reason. Assume that different genes are involved and we are crossing $\mathbf{a}_1 \times \mathbf{a}_2$. If a mutation had occurred at only one locus in each strain, which is overwhelmingly probable (why?), the mutated strain would have a normal allele at the other locus. Thus, mutant strain $\mathbf{a}_1$ would be expected to have $\mathbf{A}_2$. Strain $\mathbf{a}_2$ would be expected to have $\mathbf{A}_1$. Thus a cross of $\mathbf{a}_1\mathbf{A}_2 \times \mathbf{A}_1\mathbf{a}_2$ would produce diploid zygotes with a genotype $\mathbf{A}_1\mathbf{a}_1$ $\mathbf{A}_2\mathbf{a}_2$. Meiosis then occurs and the monoploid spores are produced. If the two loci are on different chromosomes the isolated spores should give these results:

¼ should be $\mathbf{A}_1\mathbf{A}_2$ and grow on minimal medium.
¼ should be $\mathbf{A}_1\mathbf{a}_2$ and will require arginine since $\mathbf{a}_2$ cannot function.
¼ should be $\mathbf{a}_1\mathbf{A}_2$ and require arginine since $\mathbf{a}_1$ is not functioning.
¼ should be $\mathbf{a}_1\mathbf{a}_2$ and require arginine since neither allele can function.

If the loci are on the same chromosome, the frequency of the four genotypes will depend on the amount of crossing-over.

Early on in the experiments, Beadle and Tatum discovered seven genetically different mutants, each requiring supplemental arginine if it was to grow normally. Various interpretations of the data were possible but Beadle and Tatum preferred the hypothesis that the synthesis of arginine required that at least seven normal genes be present—each producing an essential enzyme. When any one of these genes mutated in such a way that its specific enzyme could not be produced, the synthesis of arginine was blocked. There was no reason to believe, of course, that there are only seven steps in the synthesis of arginine in *Neurospora*. We can conclude only that seven was the minimum number.

It was possible to extend the analysis by taking advantage of what was already known about the synthesis of arginine. In 1932 the biochemist Hans A. Krebs had discovered that in some vertebrate cells arginine is formed from citrulline, citrulline from ornithine, and ornithine from an unknown precursor. A specific enzyme is required for each transformation.

If *Neurospora* has a similar metabolic pathway, one should be able to determine how the seven mutant strains are involved. This could be done by seeing which, if any, of the seven would grow if either citrulline or ornithine was used to replace arginine. Your students should be able to predict what conclusions could be drawn if a mutant strain, normally requiring supplemental arginine, would grow if citrulline was subsituted or if ornithine was substituted.

Many experiments were done. Four of the mutant strains would grow if either ornithine, citrulline, or arginine was added. This suggested that these four mutants were involved in reactions before the ornithine stage. If ornithine was added, the remaining enzymatic steps, being normal, could carry the reactions to arginine.

Two of the strains would not grow if only ornithine was added but they would grow if either citrulline or arginine was added. In these cases the block was between ornithine and citrulline. Since two genetically different strains were both blocked between ornithine and citrulline, it is reasonable to conclude that there are at least two steps between these molecules.

Finally, one strain was found that would grow only if arginine was added. This suggests that some enzyme between citrulline and arginine was deficient or defective.

Thus, Beadle and Tatum were able to conclude that, for *Neurospora* to synthesize arginine, a minimum of seven enzyme-controlled reactions are required and a minimum of seven kinds of molecules are involved. Two of these are known: ornithine and citrulline.

The hypothesis that a function of genes is to control the production of specific enzymes was supported. One could not conclude that this is the only thing genes do. Beadle and Tatum had designed their experiments solely to detect enzymes involved in metabolic pathways.

Much as Sutton had linked cytology and genetics in the early 1900s, Beadle and Tatum effectively linked genetics and biochemistry in the early 1940s. Their type of experimentation was used immediately by numerous other investigators on other molds, yeasts, and bacteria. This approach led directly to the molecular biology of today.

While all this was going on still another attempt to study genetics at the molecular level was underway. This was a line of investigation that began in the 1920s and ultimately led to the positive identification of the gene as DNA. That will be our final topic, bringing us to the formulation of the current paradigm of genetics by Watson and Crick in 1953.

THE SUBSTANCE OF INHERITANCE

The dynamics of scientific discovery elude us to this day. There is no way of predicting the who?, the what?, and the where? Important discoveries are nearly always made by scientists active in the field. The breakthrough may be made by an outstanding scientist or by a novice. Neither Mendel, Sutton, Morgan, Watson nor Crick was a leader in the field of inheritance to which each made such notable contributions. The revolution in biology that followed from Watson and Crick (1953*a*, 1953*b*) was due in part to scientists from other fields (mainly physics) deciding that the problems in biology were more exciting than their own (Fleming, 1968; Judson, 1979). Many prominent molecular geneticists of today remember being made aware of new possibilities for genetic research by a slender book written by Schrödinger (1945), himself a physicist.

It could be that it is easier for those not steeped in the data and traditions of a field to see problems and solutions clearly than for those fully engaged in their Kuhnian normal science. As Hanson says (1965, p. 30):

> Physical science is not just a systematic exposure of the senses to the world; it is also a way of thinking about the world, a way of forming conceptions. The paradigm observer is not the man who sees and reports what all normal observers see and report, but the man who sees in familiar objects what no one else has seen before.

Some important discoveries are the outcome of deliberate attempts to find answers to specific questions. In other cases discovery is more of an accident. The elegant experiments of Beadle and Tatum are examples of experiments planned to test a specific hypothesis. The road to DNA was not nearly so straight. The zero milestone cannot be identified but we can start in 1928 with some observations in another field that were to lead, a quarter of a century later, to the description of the chemical structure of DNA.

TRANSFORMATION IN PNEUMOCOCCUS

Pneumonia in human beings and many other mammals is caused by the pneumococcus bacterium (properly known as *Diplococcus pneumoniae*). As in many disease-causing microorganisms, there are numerous genetic strains. These are called Type I, Type II, etc. The specificity is based on the chemical composition of the bacterium's polysaccharide coat. The strains are identified immunologically. If they are injected into rabbits, antibodies are formed against the polysaccharide antigens.

If capsulated cells are grown on culture plates, they form colonies that are *smooth* and shiny. Some of the colonies may have a different appearance—they are *rough.* These changes were observed long before the cause was known—the change from *smooth* to *rough* is the result of a gene mutation. There was considerable medical interest in this phenomenon because the *smooth* cells cause pneumonia but the *rough* mutant does not. It was discovered that the *smooth* cells have the polysaccharide capsules but the *rough* cells do not.

The road to DNA begins in 1928 with F. Griffith, a Medical Officer with the British Ministry of Health. His publications give no evidence of an interest in genetics; he was a medical bacteriologist concerned with diseases of human beings. He knew that if he injected mice with capsulated Type II *smooth* (capsulated) cells, they would die. Type II *rough* (non-capsulated) cells would not cause the death of his mice. However, heat-killed *smooth* cells did not kill the mice. Therefore, it was not the polysaccharide coat that was the cause of death.

The next experiment is the crucial one for us. Griffith gave four mice a double injection of Type II cells: living *rough* cells plus dead *smooth* cells. Survival was expected, since the *rough* cells are not pathogenic and the pathogenic *smooth* cells had been killed. Nevertheless, all four mice died after five days. Type II *smooth* cells were found in their blood. Thirty control mice injected only with living *rough* cells remained healthy.

This was an unbelievable result—but the experiment was repeated and confirmed. It appeared that the ability to synthesize a capsule had been transferred from the dead capsulated cells to the living non-capsulated cells. Any geneticist of 1928 who might have known of these experiments would have shuddered and rededicated himself to *Drosophila melanogaster.*

During those years geneticists ignored microorganisms almost entirely and microbiologists ignored genetics. It was not suspected by either group that microorganisms possessed a genetic system remotely similar to that of higher organisms. Joshua Lederberg, who as a young student worked in the Zoology Department at Columbia University and who was to find that "adaptation" in bacteria is a mutational event, was far in the future.

A later generation of geneticists might have suspected that a mutation from *rough* to *smooth* had occurred but another experiment by Griffith showed this not to be so. This time the living and the dead cells were of different Types. The living cells without capsules (*rough*) were Type II and the killed cells with capsules (*smooth*) were Type I. Eight mice were injected and two died. Their blood was found to contain virulent capsulated cells of Type I. Somehow the Type II non-capsulated cells had been transformed to Type I. This was not a transitory change. They were cultured and thereafter remained Type I. The change was permanent, and hence in a broad sense genetic. In today's terms we also might suspect the transformation to virulence to be due to mutation. But this second experiment rules out that possibility since, had the living Type II cells mutated from capsule-less to capsulated, they would still have been Type II. However, the capsulated cells were like the dead cells, Type I.

This line of research was taken up by many bacteriologists, including M. H. Dawson and Oswald T. Avery of the Rockefeller Institute in New York. They became convinced that transformation must be due to some chemical substance and it was reasonable to suspect the polysaccharide of the capsule. Nevertheless that proved not to be so. Alloway, another member of the Rockefeller group, summed up the problem in 1932 as follows (with my paraphrasing):

> The polysaccharide when added in chemically purified form, has not been found effective in causing transformation of non-capsulated organisms derived from *Diplococcus* of one Type into capsulated forms of the other Type. When non-capsulated cells change into the capsulated form they always acquire the property of producing the specific capsular substance. The immunological specificity of the encapsulated cell depends upon the chemical constitution of the particular polysaccharide in the

> capsule. The synthesis of this specific polysaccharide is a function peculiar to cells with capsules. However, since the non-capsulated cells under suitable conditions have been found to develop again the capacity of elaborating the specific material, it appears in them this function is potentially present, but that it remains latent until activated by specific environmental conditions. The fact that a non-capsulated strain derived from one Type of *Diplococcus,* under the conditions defined in this paper, may be caused to acquire the specific characters of the capsulated forms of a Type other than that from which it was originally derived, implies that the activating stimulus is of a specific nature.

There is nothing in this quotation, or in the writings of other bacteriologists of the period, to suggest that transformation might be a genetic phenomenon. It seemed more probable that some sort of physiological modification had occurred. Many bacteriologists at the time suspected that some sort of Lamarckian evolution was responsible for this phenomenon known as "adaptation." It was much later that it was found that mutation and selection would account for the phenomena observed.

DNA IS THE TRANSFORMING SUBSTANCE

But if "the activating stimulus is of a specific nature," hard work and luck might discover what it is. It was found that the transforming principle could be extracted from capsulated cells and that transformation could occur *in vitro*—no need that mice be used. After a decade Avery, MacLeod, and McCarty (1944) reported that they had purified the transforming substance and that it was almost certainly DNA. The overall elemental composition of the transforming principle agreed closely with that of DNA. The molecular weight was judged to be about 500,000. The substance was highly active—one part in 600 million was effective. Treatment with trypsin and chymotrypsin left activity intact indicating that it was not protein. Ribonuclease, which denatures RNA, was also without effect. However, a then available crude deoxyribonuclease destroyed the activity of the purified transforming substance.

What does this all mean? This is how Avery, MacLeod, and McCarty interpreted their experiments (see also McCarty, 1985):

> Various hypotheses have been advanced in explanation of the nature of the changes induced. In his original description of the phenomenon Griffith suggested that the dead bacteria in the inoculum might furnish some specific protein that serves as a 'pabulum' and enables the [non-capsulated] form to manufacture a capsular carbohydrate.
>
> More recently the phenomenon has been interpreted from a genetic point of view. The inducing substance has been likened to a gene, and the capsular antigen which is produced in response to it has been regarded as a gene product. In discussing the phenomenon of transformation Dobzhansky has stated that "If this transformation is described as a genetic mutation—and it is difficult to avoid so describing it—we are dealing with authentic cases of induction of specific mutations by specific treatments . . . ."
>
> It is, of course, possible that the biological activity of the substance described is not an inherent property of the nucleic acid but is due to minute amounts of some other substance adsorbed to it or so intimately associated with it as to escape detection. If, however, the biologically active substance isolated in highly purified form as the sodium salt of deoxyribonucleic acid actually proves to be the transforming principle, as the available evidence strongly suggests, then nucleic acids of this type must be regarded not merely as structurally important [at the time biochemists could not discover any function for the nucleic acids] but as functionally active in determining the biochemical activities and specific characteristics of [the bacterial]

> cells. Assuming that the sodium deoxyribonucleate and the active principle are one and the same substance, then the transformation described represents a change that is chemically induced and specifically directed by a known chemical compound. If the results of the present study on the chemical nature of the transforming principle are confirmed, then nucleic acids must be regarded as possessing biological specificity the chemical basis of which is as yet undetermined.

Was DNA only an inducing agent or was it something else? Most geneticists would probably have agreed with Dobzhansky that DNA could not be the genetic material. The evidence was fairly convincing. Enough was known about DNA to realize that it was a rather simple molecule—composed of a few bases, a simple sugar, and phosphate. Presumably an extremely complex substance would be required to control the life of cells. Proteins were a far more likely candidate than DNA to be the gene. They could be huge and were composed of a number of amino acids about equal to the number of letters in our alphabet. Just as the combinations of a few letters can give us the uncounted numbers of words in the languages of the world, that same number of amino acids should be adequate to supply all the genetic variation required.

CORE OR COAT?

The answer came in less than a decade: DNA *is* the gene, not a mutagenic agent. One of the more important experiments was done in 1952 by A. D. Hershey and Martha Chase. By that time much more sophisticated experimentation was possible. In large part as a result of the work on the atom bomb in World War II many sorts of radioactive substances had been produced that could be used to study intracellular reactions. Methods were developed for culturing many different sorts of microorganisms and, for many reasons, they were becoming the favorite experimental organisms for geneticists. There was also very much more research being done. The extraordinary contributions of scientists to the war effort were recognized in Washington and the work of scientists began to be supported on a lavish scale. It was estimated that in the 1950s the number of active scientists was equal to all the scientists who had ever lived. Big Science was national policy and a national activity.

Hershey and Chase took advantage of the peculiar life cycle of bacteriophage to ascertain whether or not DNA contains the information for that organism. Bacteriophages, or phages, are incapable of an independent life. They are parasites of bacteria, upon which they depend for their own reproduction.

If the bacterium *Escherichia coli* is infected with a phage called T_2, the bacterium is killed in about 20 minutes. Before entrance of the phage, the bacterial cell was synthesizing its own specific molecules: bacterial proteins, bacterial nucleic acids, and so on. The phage changes all this. It assumes control of the bacterial synthetic machinery and diverts it to producing phage molecules instead of *E. coli* molecules. About 100 phages are made in about 20 minutes. The bacterium bursts and liberates the phages. They can then enter (they must if they are to live and reproduce) other bacterial cells and repeat the process.

There are many kinds of phages that maintain their genetic identity and other specific characteristics. Structurally they are simple, being composed of a protein coat and a DNA core. The protein of the phage coat is chemically very different from the DNA core. The coat contains sulfur but little or no phosphorus. The reverse is true for DNA. Radioactive isotopes of both phosphorus and sulfur were available to Hershey and Chase.

The experiment was as follows. One group of bacteria was grown in a medium with ^{32}P, which became incorporated in the bacterial molecules. Later, phages were introduced. When the bacteria then began to synthesize new phages, the latter's DNA became tagged with the ^{32}P. The protein coat would have little or no label.

In a parallel experiment bacteria were grown in a medium containing ^{35}S. This became incorporated in some of the bacterial proteins. Later phages were introduced and in this case the protein coats of the phages became labelled with ^{35}S.

These two sorts of phages, one labelled for the protein coat and the other for the DNA, were then used in separate experiments. They were introduced into cultures of bacteria and Hershey and Chase found that the labelled DNA entered the bacterial cells. The labelled protein remained on the outside. These observations, together with others, suggested that the phage attaches itself to the cell wall of the bacterium and injects its DNA core, the coat remaining on the outside.

The phages in both experiments reproduced and destroyed the bacterial cells. The experiments had shown that the entire genetic information on "how to make phage" is contained in the phage DNA.

The work surveyed in this chapter, together with a very much larger amount going on at the same time, leads to this tremendous thought: the once mysterious gene, which though invisible could be mapped and followed through the generations with precision, is revealed as an identifiable molecule—DNA. Just as E. B. Wilson had said in 1895.

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THE END

This essay, as part of the symposium *Science as a Way of Knowing—Genetics,* has sought to provide a background for the papers by the symposium speakers and to provide materials for teachers using the science as a way of knowing approach. For the most part, the speakers will be dealing with events that occurred after 1953. These events have been so staggering in their importance and different in their problems and procedures that we must recognize that a new paradigm now guides the investigators.

The old paradigm of the Chromosomal Theory of Heredity, or transmission genetics, held the attention of geneticists to the mid-1930s but by then it was so well established that geneticists sought new challenges. It was during the 1930s and 1940s the groundwork was laid for an attack at the molecular level on what genes are and what they do. Molecular genetics is very different from classical genetics, which is the concern of this essay.

And that raises a difficult problem for what should be taught in the first-year biology course in the colleges and universities when the time available is severely limited. Can Mendel, Sutton, and Morgan hold the attention of students who live in a world where genetic engineering is about to perform its miracles? Should students be taught about these classical experiments and concepts?

I think they should and there is no need for an either/or structuring of the curriculum. The basic argument of the *Science as a Way of Knowing* approach is that students are best served if they are provided with the conceptual framework of the field. Full appreciation of the events of today is possible only if that conceptual framework is understood.

There is a practical matter also. Few students in first-year courses have the background necessary to understand the tremendously sophisticated experiments and data of modern molecular genetics. In many instances they may be able to *memorize* the material but I am talking about something else—*understanding*. Classical genetics, on the other hand, is approachable to a considerable degree by students in first-year courses. They really can understand the questions, the data, and the reasons for the conclusions. This is another of our goals—having students understand how science works.

Nevertheless we serve our students poorly if we leave them ignorant of the general results and especially the implications of the science of the day. My recommendation, therefore, is to emphasize classical genetics and then discuss the main conclusions of molecular genetics, stressing its implications for better health and better food. And, most certainly, there should be consideration of some of the more difficult ethical questions that are being raised by molecular genetics.

Remember also that everything does not have to be included in a first-year course. Something of importance and interest should be left for the more advanced courses. Biologists, alone among scientists, seem to believe that all the cream has to come that first year. It really does not.

My suggestions may not have much appeal for some university scientists for according to Sydney Brenner (*Nature* 317: 209, 1985):

> For most young molecular biologists, the history of their subject is divided into two epochs: the last two years and everything else before that. The present and very recent past are perceived in sharp detail but the rest is swathed in a legendary mist where Crick, Watson, Mendel, Darwin—perhaps even Aristotle—coexist as uneasy contemporaries.

Too bad, if so. We have to do better for our students.

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Experiments in a Monastery Garden[1,2]

GREGOR MENDEL

Augustinian Monastery of St. Thomas, Brünn

SYNOPSIS. After a brief account of my early education, study at the University of Wien, and preliminary experiments on hybridization conducted at the Augustinian Monastery in Brünn, Austria, I state the reasons for selecting certain features of the edible pea, *Pisum sativum,* for extensive investigation of their inheritance. After eight years I reported my results to the Brünn Society for the Study of Natural Science, and they were published in the following year (1866) in the Proceedings of the Society. I discovered two basic principles of inheritance: the law of segregation and the law of independent assortment of hypothetical units of heredity that I called *Elemente.* I conclude with some remarks on the possible relation of my work to the evolution of organic form and on my disappointment that my studies do not seem to be known or understood, and that because of my administrative duties at the monastery, now being the Abbot, I have no time for further investigations.

Danke schön, Herr Professor Moore. Grüss Gott, meine Damen und Herren. My lecture this evening, as announced by your Vorsitzer, is on the inheritance of hybrids in the common edible pea, genus *Pisum.* My interest in heredity began already as a boy on my father's farm in Heinzendorf in Moravia, a province of Austria. My father had horses and cows, chickens and bees, peas and beans, and flowers—always flowers. Being a curious and uninhibited boy I observed breeding in animals and seed formation in plants. I found breeding of animals more interesting. I often wondered why the offspring resembled their parents but were usually not exactly like their parents. We had a good teacher in the Heinzendorf school that had opened its doors only thirty years earlier. Previously the boys and girls of Heinzendorf never learned to read or write. Their parents were too poor to send them away to school. From my teacher I learned much, including growing fruits and keeping bees.

When I completed the school my teacher told my parents that they should send me to the high school in a town many kilometers away. With great sacrifice to them I went, but it was hard to keep body and soul together. Part of the time I was on half-rations. Eventually, it appeared that I must discontinue my studies and begin to earn my own livelihood. But one of my high school teachers recommended me to the Augustinian Monastery of St. Thomas in Brünn. I was accepted and became a novice. Later I took my vows in accordance with the rule of St. Augustine. After a few years my order sent me to the University of Wien with hopes that I would pass the examinations and become an accredited teacher. Well, I did not pass my examinations, and so I returned to Brünn and became an unaccredited teacher—a good one, I am happy to say.

My interest in plants and animals, begun on my father's farm, as I have explained, continued during my school years and at the University of Wien, and became my primary preoccupation at the monastery when I was not engaged in teaching and religious duties. I always kept bees and mice. But I did not like snakes. Yet my boys brought them to me because they knew that I did not like snakes. My animal breeding in the monastery, however, was regarded as immoral by my superiors because it appeared that I was playing with sex. I had to be particularly careful not to incur further disfavor of the bishop, a conservative cleric and a very corpulent man. You see, I had made the mistake of remarking to some friends that the bishop

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[1] From the Symposium on *Science as a Way of Knowing—Genetics* presented at the Annual Meeting of the American Society of Zoologists, 27–30 December 1985, at Baltimore, Maryland.

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carried more fat than understanding. Someone reported me, and after that the bishop and I were not good friends. Incidentally, little did I know at that time that I too would acquire stout proportions. [Mendel pats his stomach.] So I turned from animal breeding to plant breeding. You see, the bishop did not understand that plants also have sex. *Gelt*?

I had long grown ornamentals for their lovely flowers, and I had learned to cross-pollinate them to obtain interesting hybrids. But these plants were not suitable for the study of inheritance. After trying several kinds of plants I found that the common garden pea was most satisfactory, for several reasons. First, seeds of several varieties could be obtained from seedmen in the town. Second, the plant grew well in the little plot assigned to me in the monastery garden. Third, its flower is ideally constructed for experiments in hybridization. Normally the plant reproduces by self-pollination. But this can be prevented by removing the stamens, the male organs, before the pollen is ripe. The flower is like this. [Mendel uses his hands to illustrate.] Simply spread apart the petals to reveal the sex organs inside. Pull out the stamens with a pair of tweezers, leaving the pistil, the female organ. Cross-fertilization can then be accomplished by dusting pollen from a ripe flower on the pistil by means of a small brush. The petals enclose the pistil so well that fine airborne pollen cannot enter. Thus the chances of contamination are slight, but I never relied on it. There is the pesky pea weevil that can enter the bedroom chamber. So I always tied paper bags over the flowers in my experiments. And four, there are other advantages to peas. They are nutritious. I usually carry a pocketful of them to satisfy my yearning. [Mendel produces handful of peas from his clerical gown and pops some into his mouth.] And when my boys pay no attention to my lectures or they fall asleep, I simply ask the Almighty to send down a shower of peas. [Mendel peppers his audience with peas.] That wakes them up! *Gelt*?

After a few years of preliminary studies to test the purity of my seeds and to select features for study I began my experiments in earnest in 1856 and finished them eight years later, after studying over 10,000 pea plants. I presented my results in 1865 to the Brünn Society for the Study of Natural Science, and they appeared in the *Proceedings* of our society in the following year.

I found that some features had clear contrasting traits such as tall and short vine or either red or white colored flowers. In all I selected for study seven features with clear and distinct traits. The seven that I chose were color of seed, shape of seed, color of pod, form of pod, color of flowers, position of flowers on the stem, and length of stem. For each of these features one of the traits was dominating and the other was recessive. For example, red flower was dominating over white flower; and tall vine was dominating and short vine recessive. I illustrate what I mean by dominating and recessive.

I have here some red and white sweet pea blossoms. Let us assume that they are flowers of the garden peas. Now I cross a red-flowering plant with a white-flowering one. [Mendel playfully rubs together red and white plastic blossoms and looks up at his audience with a grin.] It makes no difference in the results whether I dust the pistil of the red flower with pollen from a white one, or *vice versa*. All of the next generation plants have red flowers, one hundred percent—not a single white flower. Now, is the white trait lost? No! When I cross two of the first generation plants, lo and behold white flowers will appear in all their purity. The whiteness was only suppressed by the redness, and that is why I call white recessive and red dominating.

Of course, there were red-flowered plants in the second generation offspring. When I counted them there were about three of the reds for every one of the whites. The ratio is about 3 to 1. Now I say "about"—it was never exactly 3 to 1. As examples, I quote from my paper. In one experiment I had 929 plants: 705 had red flowers, 224 white ones. The calculated ratio was 3.15 to 1. In another instance, the ratio was 2.95 to 1. I think that if I had produced more plants my ratios would probably be closer to the theoretical 3 to 1.

I now proceed to analyze the second-generation plants. We discover, not unexpectedly, that the white plants when crossed with white give white flowers. Actually, it is easier to allow a white-flowered pea to self-pollinate. Thus pollen from a white flower fertilize ovules in a white flower. Obviously, the whites are a pure line. Consider now the red-flowered plants: one third of them turn out to be pure red-breeding. When crossed with each other, or when you permit self-pollination, they produce only red-flowered plants, just like grandfather. The other two-thirds of the second generation reds are like father and mother—hybrid red—because upon interbreeding they give a 3 to 1 ratio of red to white. So you see we have actually three kinds: pure red, hybrid red, and white. And the ratio between the kinds is 1:2:1. *Gelt*?

[Mendel suddenly notices a stem with pink flowers. He picks it up.] *Ach du Lieber*! *Was ist das*? Pink flowers? They should be only red or white! [He tosses the pink flowers away.] I think that some student has played a trick on Pater Mendel. *Also*! I began to think of discrete hereditary units. I called them *Elemente*. They pass from generation to generation through the pollen grains and the ovules. Now there must be an *Element* for whiteness, a recessive, and a dominating *Element* for redness. When they are together in a hybrid, the flowers are red. But the *Element* for whiteness is there, all the time. It will not be lost or contaminated. I then devised a simple system for recording the *Elemente*, to save much writing. I said let the letter A represent an *Element* for flower color with capital *A* standing for the dominating *Element* and little *a* for the recessive *Element*. Now hybrid red, because it has both *Elemente*, should be expressed by *Aa*. When the hybrids produce pollen and ovules the *Elemente* separate from one another so that in the stamens two kinds of pollen grains are formed, half of them possessing large *A* and half of them little *a*. Likewise in the pistil two types of ovules will develop: those with *A* and those with *a*. *Gelt*? This separation of the *Elemente* I called the law of segregation.

You must understand that I was not the first person to study inheritance. Men and women have been breeding plants and animals since ancient times and some scientists have tried to discover the principles of heredity. But why did I succeed whereas others failed? One reason is just this: I selected a few features with well-defined, contrasting traits to study in an organism that was suitable for experimentation. My predecessors, however, tried to study the whole organism at once. But inheritance is complex. One must simplify the investigation, study one pair of contrasting traits at a time. And then you may study two traits together, as we shall do presently. Only in that way can one discover the secrets of nature. Then second, I used quantitative methods. I counted peas, and peas, and peas! I kept very careful records, and I calculated ratios. During the long winter months I worked with my seeds, counting them, placing them in properly labeled envelopes, posting my accounts, doing the calculations, and planning the experiments for the next spring. Hard, tedious labor, but that was how I succeeded. I shall not say that my predecessors were lazy. I was willing to work with zeal, patience and with the stubbornness of my peasant ancestry.

Also. Having studied all seven features with clear contrasting traits and learning that each one obeys the law of segregation, I proceeded to study two or three features simultaneously. Let me illustrate. Suppose we cross a pure-breeding red-flowered, tall pea plant with a white-flowered, short one. Now we must choose a letter to stand for length of vine, the second feature. Choose letter B. Again the large *B* represents the dominating *Element* for tall; the little *b* stands for the recessive one for short. So I write *AABB* × *aabb*. All of the first-generation offspring will be hybrid red and hybrid tall or *AaBb*. *Gelt*? This follows from the law of segregation.

Now let us cross two such hybrids or simply allow self pollination. I then discovered my second principle, the law of independent assortment. That means the *Elemente* for one feature (flower color) segregate independently of the *Elemente* for the other feature (length of vine). Thus there are four types of pollen grains: *AB*, *Ab*, *aB*, and *ab*; and there are the same four types of ovules. Next, we analyze the second-generation offspring. [Mendel uses a Punnett square—an anachronism—to explain the four phenotypes and nine genotypes and their ratios. And with a table he demonstrates the arithmetic progression in numbers of gametes (pollen and ovules), phenotypes (traits), and genotypes (kinds), and the combinations of gametes in crosses of hybrids.]

Also! What are these discrete *Elemente* about which I have been speaking? I wish I knew. My microscope does not greatly magnify. I can see the tiny pollen grains but not the *Elemente* inside them. I hope that someday a powerful microscope will be invented so that we can see the elements of inheritance. And perhaps someday clever chemists will be able to tell us their chemical composition. Much more work needs to be done on inheritance.

Recently I had a conversation with some visitors in the monastery garden. One member, a botanist, asked: "What is the relationship, if any, between your work and the origin of a new species?"

"I am convinced," I replied, "that my studies on hybrids are of significance for the evolutionary history of organic form."

They pressed me further. "Was I acquainted with the writings of Charles Darwin?" "Yes, indeed," I said. "I have read almost everything that he has written on the subject of evolution. Our monastery library contains many of Darwin's books and also *Zoonomia* by his grandfather, Erasmus Darwin."

"I have long thought that there was something lacking in Darwin's theory of natural selection. And I have also questioned the views of Lamarck. I once made an effort to test the influence of environment on plants. I transplanted certain plants from their natural habitat to the monastery garden. Although cultivated side by side with the form typical of the garden, no change occurred in the transplanted form as a result of the change in environment, even after several years. Nature does not modify species in that way, so some other forces must be at work."

My visitors then asked me about new experiments that I was conducting. I sadly looked about the garden. Not one of my plants could be seen. All were gone. I have become so burdened with the administration of the monastery that I no longer have time for experiments. Much of my time and energy is required to fight the state government for money to educate my boys. The government does not seem to realize the importance of education. Maybe this is your experience also. And I have become discouraged. Few appear to know about my work—not even Charles Darwin. But I take comfort in the thought that science is always moving forward, although slowly at times. Sooner or later—sooner or later—my work will be repeated, and I shall be either right or wrong. In the meantime I must have patience. I think that my day will come. That is what I tell my boys. I say to them: "Work hard, work with joy, and work with patience. And I often commend to them that verse in the Book of Ecclesiastes: "The patient in spirit is better than the proud in spirit. Therefore, be not hasty, and be not angry: for haste and anger rest only in the bosoms of fools." May God bless you.

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On the Origin of Mendelian Genetics[1]

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SYNOPSIS. An examination of research on heredity in the years between Mendel's scientific work and his multiple rediscovery (approximately 1850–1900) suggests that at the turn of the century the elucidation of the mechanism of the transmission of hereditary traits from parent to offspring was inevitable. By 1900, a variety of different investigators were either attacking the problem of genetic transmission directly and successfully, or were examining specific aspects of the issue. However, it appears that the identity of analysis used by Mendel and by his rediscoverers was primarily the result of the latter all following Mendel's formulation. Had Mendel not been rediscovered, the "Laws of Heredity" would likely have been formulated quite differently, and been discovered and refined over a period of time rather than all being discovered and given their final form at the very outset.

INTRODUCTION

The tradition fostered by almost all textbooks of Genetics has it that an Austrian monk named Gregor Mendel, working alone in the garden attached to his monastery in the city of Brünn (now Brno) for some eight years, succeeded in elucidating the laws governing the transmission of hereditary traits from one generation to the next. These discoveries were communicated in a series of two lectures delivered to the Natural History Society of Brünn in 1865, and in a paper, *Versuche über Pflanzenhybriden,* published in the Proceedings of that Society for 1866.

Despite containing what we now know to be a correct interpretation of the mechanism for the transmission of hereditary characters, clearly presented and convincingly proved, Mendel's work was ignored by his contemporaries and lay in almost complete obscurity for the next thirty-four years. Then, in 1900 both Mendel's paper and his principles of inheritance were independently rediscovered by three European botanists: Hugo de Vries working in Holland; Carl Correns in Germany; and Erich von Tschermak in Austria. It is from this multiple, simultaneous rediscovery that the contemporary science named Genetics in 1906 dates.

The reason for the long neglect of Mendel's work has been a continuous source of intense historical curiosity since 1900. The problem is particularly perplexing because none of the obvious reasons for the neglect—that Mendel was a nonprofessional who worked in an intellectual backwater and was thus unnoticed by the contemporary scientific community, that the rediscoverers' technical approach was better or perhaps easier than Mendel's, so that Mendel's paper was not understood by his contemporaries, that Mendel's paper simply was not seen because it was published in an obscure journal—do not seem to obtain.

The region known as Moravia was in Mendel's time a small part of the vast Austro-Hungarian Empire, but it was by no means a scientific or intellectual backwater. In the early part of the nineteenth century there were already many active agricultural and academic societies dispersed throughout Moravia (Franke, 1983; Orel, 1983). Among the members of these societies, there was an active interest in animal breeding and plant hybridizing stemming from the increased economic importance of the sheep industry and the need for increased production of cereal grains. This interest, moreover, was not confined to the practical, but also encompassed a strong theoretical vein inasmuch as the Moravian breeders were anxious to discover the theoretical rules of heredity by means of which they could convert the art of breeding into

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a science. Nor was the interest in breeding and hybridizing reserved for agricultural commodities (Vavra and Matalova, 1983). Studies indicate that in Moravia there was a lively interest in the use of artificial fertilization for the production of ornamental plants—an area of some significance in Mendeliana because it was Mendel's observations on the breeding of ornamental plants that led to his undertaking the study of plant hybridization in an effort to determine the laws governing the formation of the hybrid.

Moravia not only possessed agricultural and academic societies which encouraged the study of breeding, but there were even courses on practical breeding and heredity introduced into the university curriculum (Wood and Orel, 1983). Moreover, there was lively interchange between Moravia and such scientific centers as Prague (Janko, 1983). Finally, even the image of the Augustinian monastery in Brünn as a secluded retreat must be considerably modified. The monastery with which Mendel was affiliated had been specifically directed by an imperial decree of 1802 to devote itself to the teaching of science in schools of higher learning. The monks, moreover, were not merely teachers of science but also practitioners of scientific research, especially in the area of plant hybridization (Orel and Fantini, 1983). It was, in sum, this stimulating, in a sense central, and clearly scientifically charged community which provided the framework for Mendel's own scientific development and fulfillment.

With respect to the approach that Mendel took, it turns out that none of the rediscoverers report experiments nor introduce concepts that are different from those found in Mendel's paper thirty-four years earlier. Indeed, Mendel's data are in all cases more numerous, and, read today, his arguments are more complete, clearer, and more compelling than those of the rediscoverers. Significantly, the rediscoverers followed Mendel's analysis almost exactly point for point.

Finally, the suggestion that occurs most readily to the modern scientist, namely that the neglect of Mendel's paper is a consequence of the obscurity of the *Verhandlungen des naturforschender Vereines in Brünn,* has mainly been discounted by modern scholarship (see, for example, the papers of Glass, 1953; Dodson, 1955; Gasking, 1959; de Beer, 1964; Zirkle, 1964; Posner and Skutil, 1968; Weinstein, 1977). In the first place, the Brünn Natural History Society had exchange publication arrangements with over one hundred universities and scientific societies, so that Mendel's paper was available to all the biologists connected with these institutions. Thus, for example, the three rediscoverers, working independently and in separate countries, each found Mendel's paper before publishing any original results on the subject. Moreover, even before the rediscovery, Mendel's paper did not go entirely unremarked. It was cited in an article by the German hybridist H. F. H. Hoffmann (1869); it was included in a widely diffused, widely read monograph on hybridization by the German W. O. Focke (1881); it was referred to in an article on hybridism in the ninth edition of the Encyclopedia Britannica; and it was listed in the extensive bibliography amassed by the well-known American breeder L. H. Bailey (1892).

It would seem, then, that the more than thirty-year neglect of Mendel's work must be ascribed to some conceptual obstacle or obstacles not finally overcome until 1900. Among such conceptual obstacles, the following figure as most important in the historical literature. First, during the whole of the second half of the nineteenth century, biology as a discipline was principally concerned with the problems of evolution that had been raised by Mendel's contemporary, Charles Darwin. Issues unrelated to the origin of species were, at that time, difficult to see as important and might, on that account, be ignored (Iltis, 1932; Wilkie, 1962; Stubbe, 1972). Although it seems obvious to us today that Darwinian evolution theory was inadequate, requiring Mendelism for its logical completion, that interpretation did not become obvious until after that second decade of the twentieth century (Provine, 1971). To nineteenth century biologists, variation within a species was simply not as important an object of study as was variation among species, and to this latter issue Mendel had not paid particular attention.

However, the attitude that the problem of inheritance was not of the first importance, while likely influential, cannot by itself explain the neglect of Mendel. Many nineteenth century biologists, most notably Darwin himself, produced theories of heredity which, although they ultimately proved incorrect, were not ignored. Indeed, Yves de Lage recorded over thirty different theories of heredity which appeared in the scientific literature between the mid-1860s and the mid-1890s (de Lage, 1903). (It should perhaps be noted that de Lage did not include Mendel's theory in his compendium!)

Probably, therefore, of more consequence to Mendel's neglect than the domination of nineteenth century biology by evolution theory were the novel aspects of Mendel's attack on the problem of heredity. Mendel deduced his fundamental proposition, the law of segregation, from the results of classifying and counting the progeny of controlled matings. He showed that the ratio of the number of one progeny type to its alternative was always consonant with expectations based on the random fusion of gametes, one-half of which contained one of the determinants and the other half the alternative determinant carried by the parents. The mathematical and statistical concepts that Mendel employed in this demonstration were all well known to nineteenth century science, but they were rarely employed by biologists, and their use as fundamental components in Mendel's arguments likely made these arguments too abstruse for many (Dodson, 1955; Wilkie, 1962; Dunn, 1965; East, 1967). However, it should be stressed that no matter how appealing this argument might seem, it too cannot represent the whole solution to Mendel's neglect. In the first place, nineteenth century science was very receptive to mathematical methods and ideas. This tendency to mathematization in the sciences is reflected in the view expressed by the nineteenth century historian, John Merz, writing on European scientific thought in this period. Modern science "is based upon numbering and calculating—in short, upon mathematical processes; and the progress of science depends as much upon introducing mathematical notions into subjects which are apparently not mathematical, as upon the extension of mathematical methods and conceptions themselves." More specifically, contemporaneously with Mendel's publication, Francis Galton, in England, wrote *Hereditary Genius* (1869) which was a wholly mathematical treatment of heredity. Nevertheless, it was not neglected at all; on the contrary, it became the focus of widespread discussions and the subject of many critical reviews (Sandler and Sandler, 1985).

Probably even more difficult to comprehend in those years was Mendel's definition of the problem of heredity. In the nineteenth century, the conceptual distinction between the inheritance of a character and the embryological development of that character, so obvious to modern science, was hazy at best (Sandler and Sandler, 1985). "Inheritance must be looked at as merely a form of growth," Darwin wrote in his very influential book, *The Variation in Animals and Plants under Domestication*, and this idea, the view that inheritance was simply a particular moment in embryological development and not a distinct process requiring its own analysis, was shared by the vast majority of Darwin's, and therefore of Mendel's contemporaries and immediate successors. It seems that the distinction between the set of concepts that are today studied under the aegis of "genetics" on one hand and "embryology" on the other, is a twentieth century distinction. Gregor Mendel's 1866 paper dealt entirely with the subject of the transmission of inherited traits (that is, with Genetics) and therefore would have seemed to his contemporaries a partial work, a work that could not have contained a theory of inheritance. Indeed, it is clear from the few extant references to Mendel's work that his experiments were not seen as providing evidence for a theory of heredity; rather his observations on hybrids were appreciated as being useful only in the same way as were the observations of other nineteenth century hybridists who, in fact, did not develop theories of heredity. It may be this separation of the transmission from generation to generation of a character from its behavior within any one generation (development) that, more than anything, prevented Mendel from being understood until so long after his work was presented to the scientific public.

In any event, whatever the reason or reasons that Mendel's work lay unappreciated for more than thirty years, the observed chronology of events—*i.e.*, the long period of obscurity followed by the simultaneous, multiple rediscovery—seems to contain two implications about the way science develops. On the one hand, a long obscurity followed by a multiple, simultaneous rediscovery suggests that there is a time—a time that is in some sense independent of human investigators—when each effective discovery will be made. Before that moment, the world is not ready and the discovery, even if accomplished, will not be effective. At that moment, the discovery will be made by one investigator or another from a pool of workers all approaching the answer, so that after that moment it is too late for original work. Clearly, for the discovery of the laws of inheritance, that moment was 1900.

The second implication comes from the nature of Mendel's analysis and that of the rediscoverers. In each case, the form that the laws of heredity took was almost exactly the same. This seems to suggest that the laws of inheritance have, in some sense, an objective existence in nature, and that what each scientist has done is simply to have found, or discovered this preexisting truth. Thus, the identity of approach by Mendel and the three rediscoverers could be understood as the result of each having discovered the selfsame objective natural truth.

An examination of the history of investigations into the problem of heredity from the period of Mendel's work until its rediscovery (*ca.* 1850–1900) reveals that, indeed, an understanding of the transmission of characters from generation to generation would inevitably have come with the new century. The oft-cited rediscoverers were but three in a rather sizable group of investigators who were contributing to, or independently approaching, an understanding of hereditary transmission in the years just before 1900. However, the form that this understanding took varied considerably from worker to worker, so that the uniformity that ultimately developed is primarily a tribute to Mendel's genius, and at most in a minor way reflective of the existence of some objective reality. That is, had Mendel's work not come to light in 1900, it seems likely that the form that early Genetics would have taken would have been quite different from that which we know.

> *For everything there is a season,*
> *and a time for every matter under heaven . . .*
> *a time to seek . . . a time to speak.*
>
> Ecclesiastes 3

THE SCIENCE OF HEREDITY IN 1900

Had Gregor Mendel not performed his experiments with the pea plants or had his work not been rediscovered in 1900, evidence indicates that a science of genetics would still have been articulated, though perhaps not with the same elegance, precision or coherence that characterizes Mendel's legacy. The purpose of this section is to examine how the science of genetics was evolving during the nineteenth century, without the benevolent guidance of the Augustinian monk. Indeed, quite independently of Mendel, and quite independently of each other, two groups of workers, the hybridists and the cytologists, were making observations, accumulating information and shaping knowledge so that by the turn of the century, each group had arrived at equivalent positions; namely, the point at which each group could enunciate a law of segregation, the basis of the study of formal or classical genetics.

This gradual synthesis of the foundations of genetics by the scientific community (as opposed to the sudden, unexpected confrontation of the scientific community with Mendel's complete and revolutionary opus) meant that when Mendel's work was rediscovered and once again offered to scientific scrutiny, the time was ripe for a proper appreciation of its contents as measured by the immediate enthusiasm with which the Mendelian laws were put to use in examining heredity in plants and animals.

It could be argued that seeking to reconstruct the piecemeal development of Mendelian genetics without Mendel is an unnecessary exercise. After all, we have only to recall that the rediscovery of the Mendelian laws and Mendel's paper was the achievement of three investigators—Correns, de Vries and Tschermak. Surely, by simply examining these three works, we should be able to observe the leap that had been taken from the pre-Mendelian to the Mendelian era, since each of the rediscoverers claims to have arrived at his conclusions independently of the others and quite independently of any knowledge of Mendel's work.

However, the independence of Correns, de Vries and Tschermak from Mendel's influence remains a moot point. Contemporary opinion discounts Tschermak as a genuine participant in the rediscovery of Mendel's laws. "Tschermak's papers of 1900 not only lack fundamental analysis of his breeding results but clearly show that he had not developed an interpretation" (Stern, 1966). Moreover, whether or not Correns and de Vries actually succeeded in unsnarling the tangle of hybrid inheritance before having read Mendel's paper is also a subject of considerable dispute. If one examines the papers that each of them wrote prior to 1900, there is little which foreshadows a Mendelian view. In addition, since the rediscovery papers are couched in Mendelian terminology, it is very difficult to extract the particular ideas that Correns and de Vries postulated about the nature of the transmission of hereditary traits prior to having been exposed to Mendel's theories. Consequently, to trace a sequence of events that leads to a non-Mendelian interpretation of the law of segregation, it is reasonable to eliminate the rediscovery papers themselves from consideration.

THE PATH OF THE HYBRIDISTS

One of the innovative features of Mendel's work was his approach to producing hybrids. Although hybridists had been crossing species and varieties for over a century, it was Mendel who insisted on the purity of the parental lines, who required that an extended number of generations be derived from the hybrid progeny, who maintained that records be kept of the different kinds of progeny produced from each cross and of the numbers of individuals in each class so that one could assess the numerical relationships among the different classes produced.

Until the middle of the nineteenth century, plant breeders sought to improve crops chiefly through the method of selecting seed from the best fruits and grains. Little attention was paid to the parentage of the seed. Seeds were planted, allowed to fruit and then were examined. Those which produced the most desirable fruit or the largest grains were propagated. The practical advice given to breeders was that one "plant the best seeds of the finest varieties, take good care of the plants and trust to Providence for the result" (Webber, 1899).

In the middle of the nineteenth century, breeders had begun turning to the method of hybridization as a means of improving domesticated plants. This involved the crossing of two plants sufficiently different to be considered distinct species. Of particular importance, however, was the fact that both parental lines were known to the breeder. Should the progeny of a particular cross not bear the desired combination of characters, the hybrids were crossed once again to produce a second generation of hybrids, and if necessary successive generations were produced in order to obtain the desired results. Observations provided by breeders indicate that hybrids were almost always uniform in appearance and intermediate in character between the parental forms. The production of progeny from such hybrid parents "often consisted of a few forms nearly like the (original) parents and numerous forms representing all grades of intermediates" (Swingle and Webber, 1897).

In addition to providing verbal descriptions of the hybrid progeny, by the last decade of the nineteenth century, breeders were starting to include numerical descriptions of the progeny. In 1891, the first genetic ratio actually counted and recorded had appeared in a paper by Kellerman and Thompson which involved the crossing of a variety of blue kernel corn to a white kernel variety. In their results, the breeders called attention to the prepotency of the blue color over the white and provided numbers to emphasize the preponderance of blue to white plants: 277 blue to 93 white (a perfectly good 3:1 ratio, reports Singleton, 1935).

This work of Kellerman and Thompson was part of a general movement among corn breeders to develop improved varieties of maize, but the hybridization of the corn varieties yielded much more than improved strains of hybrid corn. The breeders were quickly alerted to a phenomenon which was both startling in its effects and inexplicable as to its cause. They observed that in the pollination of a female plant by pollen from another strain, there appeared to be an immediate influence of the pollen parent on the endosperm tissue of the newly formed seed, tissue which was thought to have originated entirely from the maternal plant. This phenomenon, called xenia by Focke (1881), had been demonstrated earlier by the French botanist and breeder, Henri de Vilmorin (1866) and the German botanists, Hildebrandt (1867) and Kornicke (1872). Interest in xenia was demonstrated in the United States by Burrill (1877) and Tracy (1888), each of whom had conducted experiments affirming that pollen of one strain could influence the endosperm of another strain. Because xenia was so frequently an unavoidable consequence of a hybrid cross, many corn breeders in the last quarter of the nineteenth century found their very practical work dove-tailing with those investigators who were primarily interested in examining the phenomenon of xenia for its own sake. From these breeders, however, some very interesting and valuable observations were becoming incorporated into a growing pool of knowledge about inheritance in plants. Thus, Willett Hays, working at the Minnesota Agricultural Experiment Station in 1888, crossed a strain of corn which possessed a starchy endosperm (kernels are smooth and round) to a strain of sweet corn (such kernels are shrunken and wrinkled). Seeds from such a cross were planted and then the grown hybrids were crossed by controlled pollinations. The kernels on the ears produced by these plants were described by Hays as showing ¼ sweet kernels and ¾ starchy—a clear instance of segregation. In another set of experiments, Hays used a plant bearing yellow, round kernels as the female parent and crossed it to a plant that showed purple, wrinkled kernels. His workers were told to save any ears which, like the female parent, showed smooth kernels and also exhibited purple coloration (an obvious demonstration of xenia). Hays observed, "In no case had the sweet variety given these grains the rough form of the sweet corn but merely the color, while in form and hardness they resembled the female parent" (Singleton, 1935). These kernels were planted and the plants allowed to cross-fertilize. Hays noted that not only had he obtained the black, sweet kernels and the yellow, starchy kernels characteristic of the original parental strains, but he also obtained yellow, sweet kernels and black, starchy kernels. Although no numbers were given, what Hays was describing was a straightforward instance of independent assortment. Moreover, Hays went on to say that "The color of the black, starchy grains can be explained by assuming that the smooth parent form was predominant, while the color of the sweet prevailed." Hays was observing both dominance and independent assortment.

Kellerman and Swingle (1889), working in the Kansas State Agricultural Station, hybridized strains of yellow and white corn in one set of experiments, starchy and sugary corn in another series of crosses. Each set of experiments was followed to the second generation where the hybrid progeny were examined. Although no accurate count was made of the progeny types, they did estimate a 3:1 ratio for the yellow : white and starchy : sugary traits (Singleton, 1935).

These are merely two instances of the type of corn hybridizing work that was being done by the breeders of the time.

And although the requirements of their breeding programs did not call for a careful counting of the various kinds of kernels that were produced on each ear, some breeders did provide an overall impression of the relative proportions of the different kinds of kernels produced. What is of special importance, however, is the fact that these breeding programs and the associated appearance of xenia sensitized so many workers to the Mendelian phenomena of dominance, segregation and independent assortment. No longer were such kinds of behavior the isolated observations of a select few. On the contrary, reports of the Mendelian behavior of the endosperm characters were now commonplace and this had the effect of preparing the members of the breeding community to accept the occurrence of the same kind of behavior as described for characters which were not associated with xenia. A sense of the potential significance of xenia is hinted at in the statement by Webber (1897) in which he observed that "these curious effects of foreign pollen . . . are not as yet known to be of any great practical importance" but they could be "of the greatest interest to the student of heredity."

Among such students of heredity, we can include Correns, de Vries and Webber himself. Each of them set up a long range program of crosses for the express purpose of studying xenia and its cause (Correns, 1899; de Vries, 1899; Webber, 1899). Each of them was scrupulous in establishing, maintaining and testing the purity of the parental lines. There was also close agreement from each piece of work in the observations made and the conclusions reached. These investigators, like the breeders, observed that xenia did not always occur—*i.e.*, the character of the pollen parent was not always visible in the seed. However, they did not stop with this observation. Each determined that xenia occurred when the pollen plant carried the purple color for the kernel or carried the starchy type endosperm. If the female parent were dark and crossed to a yellow pollen parent, no influence of the male parent was seen. Similarly, if the female plant produced starchy endosperm, the pollen parent from a sweet variety had no effect on the appearance of the kernel. Interestingly enough, the three investigators, while aware of the non-reciprocal nature of the crosses with respect to the endosperm characters, did not speak of the prepotency or dominance of one trait over the other; they merely noted the lack of success of the modifying ability of the pollen parent.

Each of the three botanists also observed the segregation of the endosperm characters in the hybrid progeny and commented on the assorted combinations of the two endosperm characters of color and form when the parental lines differed in both traits. No explanation was given. However, when Correns, de Vries and Webber demonstrated that when xenia occurred the embryo in the seed was also hybrid, the explanation for this regularity was not delayed in coming. Nawaschine (1898) and Guignard (1899), both cytologists, had recently shown that in higher flowering plants, not only do the nuclei of sperm and egg meet to form the embryo, but that there is also a fusion of the two pole nuclei of the embryo sac with the generative nucleus of the pollen tube. Thus, two fertilizations had occurred—one to form the embryo, the other to form the endosperm. Correns, de Vries and Webber were able to demonstrate that the endosperm fertilization was a true fertilization because the endosperm tissue was also hybrid. It contained the nuclear contributions from the paternal and maternal parents. Thus, when the pollen came from a dark and/or starchy strain, the endosperm was likewise dark and/or starchy.

In 1899 then, Correns, de Vries and Webber had made the connection between double fertilization and double hybridization, and they had described, but not defined, dominance, segregation and independent assortment for two endosperm characters. The next critical step, *i.e.*, recognizing that the behavior of the characters in the endosperm mirrored the behavior of the characters of the embryo, was not taken by these researchers in 1899. But just one year later, and making use of the same data that had been collected from the xenia studies, Correns and de Vries each made an inspired leap out of the shadowed confusion of the nineteenth century studies of inheritance to the threshold of the twentieth century and the beginnings of genetics.

One of the major obstacles to an appreciation of the significance of Mendel's work by his contemporaries was a conceptual one. For the most part, biologists of the nineteenth century tended to regard heredity and development as two aspects of the same biological process. A treatise on heredity automatically involved a discussion of development (Sandler and Sandler, 1985). Mendel sharply broke with this tradition by unlinking the study of heredity from the study of development. He chose to examine only the transmission of traits from parent to offspring and to this end he developed a method of analysis which would enable him to follow the appearance of a character in successive generations. By thus separating the transmission of characters from their development, Mendel had inaugurated the study of heredity as a discipline in its own right.

The growth of an interest in heredity per se received impetus from the research into xenia. After all, xenia focused exclusively on transmission, namely, the passage of a trait from the male parent to the progeny. However, quite apart from xenia studies in plants, there seems to have been a growing interest in the inheritance of particular traits in a variety of organisms. Thus, a nine year study of the inheritance of deafness in humans appeared in book form, entitled *Marriage of the Deaf in America,* by Edward Fay (1898); the *American Naturalist* carried a notice of the research by R. Anthony in the inheritance of taillessness in Manx cats (1899); G. von Guaita studied seven generations of white and waltzing mice (1899); *Popular Science Monthly* (1900) reported on the work of C. O. Whitman in pigeons, carried out "as a means of studying the phenomena of heredity shown in hybrid forms . . . . Biologists everywhere are coming to realize the necessity of systematic and continuous study of families of animals through a number of generations." The hereditary transmission of traits was coming to be thought of as an autonomous area of scientific investigation. "The central problem of heredity is to form some conception of what we have called the relation of genetic continuity between successive generations; the central problem of inheritance is to measure the resemblances and differences in the hereditary characters of successive generations, and to arrive, if possible, at some formula which will sum up the facts . . . while it is interesting to inquire into the orderly and correlated succession of events by which the fertilized egg cell gives rise to an embryo, this is the unsolved problem of physiological embryology" (Thomson, 1900).

Mendel, in the introduction to his paper on plant hybrids, stated that he was very impressed by "the striking regularity with which the same hybrid forms always reappeared whenever fertilization between like species took place." He was determined to learn the reasons for this regularity and to achieve this understanding, Mendel realized that the kinds of experiments he would need to perform were those which would enable him "to determine the number of different forms in which hybrid progeny appear, permit classification of these forms in each generation with certainty and ascertain their numerical interrelationships." Clearly, his program of research had a decidedly quantitative, mathematical bent to it. This mathematical approach is even more apparent in Mendel's description of the behavior of the paired alternate characters. Mendel believed that the paired factors were obliged to separate from each other at the time of gamete formation. At the same time, each pair of factors behaved independently of the other factors. Mendel realized that he would be able to use the law of combination to describe the composition of the mature germ cells and he could apply the laws of probability in predicting the kinds of progeny produced from each cross and the ratio of the progeny types to each other.

Although many biological issues did not prompt many nineteenth century investigators to make use of mathematics in their research, there was, as mentioned before, a growing mathematization of biology. This current is particularly noticeable in the study of inheritance, and the person most credited with establishing statistics as an effective method in the analysis of inheritance is Francis Galton.

Just as Mendel was struck by the regularity of progeny types apparent in hybrid populations, so did Galton remark on the "curious regularity commonly observed in the statistical peculiarities of great populations during a long series of generations" (Galton, 1889). And just as the focus of Mendel's work was on the transmission of traits from parents to offspring, using the laws of combination and chance to predict the classes of progeny, so too was it Galton's intention "to show the large part that is always played by chance in the course of hereditary transmission, and to establish the importance of an intelligent use of the laws of chance and of the statistical methods that are based upon them, in expressing the conditions under which heredity acts."

This application of statistics to the study of heredity was regarded in a distinctly favorable light by the turn of the century. In his speech to the Royal Society in March 1900, J. Arthur Thomson declared, "In the development of natural knowledge, science begins where measurement begins. This is the case in regard to inheritance. While nothing can take the place of experiment, much has been gained by the application of statistical and mathematical methods to biological results—a new contact between different disciplines—which we may particularly associate with the names of Mr. Francis Galton and Mr. Karl Pearson."

The school of biometry, however, as envisioned by Galton and Pearson, tended to appeal more to the mathematicians than to the field biologists. It was William Bateson who took on the task of adapting methods of statistics to the needs of the biologist; and it is in his talk on hybridization read to the Royal Horticultural Society in July 1899, that Bateson comes so close to echoing the ideas of Mendel. "What we first require is to know what happens when a variety is crossed with its nearest allies. If the result is to have a scientific value, it is almost absolutely necessary that the offspring of such crossing should then be examined statistically. It must be recorded how many of the offspring resembled each parent and how many showed characters intermediate between those of the parents. If the parents differ in several characters, the offspring must be examined statistically, and marshalled, as it is called, in respect of each of those characters separately. Even very rough statistics may be of value . . . . Detailed and full statistics can only be made with great labor, while such rough statistics are easily made. All that is really necessary is that some approximate numerical statement of the result should be kept." It was Bateson's strong belief that carefully recorded hybridization experiments of the kind he was endorsing "would in some five-and-twenty years make a revolution in our ideas of species, inheritance, variation and other phenomena which go to make up the science of Natural History."

The revolution that Bateson conjectured on was even closer at hand. Three thousands miles away, in a symposium held in Washington, D.C. in 1900, an American agricultural scientist, W. J. Spillman, reported the results of experiments in which he made controlled crosses among a variety of strains of wheat, and, like Mendel, counted the number of each type of offspring that resulted. Spillman, although to be sure he saw considerably less clearly and less far than did Mendel, analyzed his results brilliantly and surely.

He saw in the regularity of the observed results that "perhaps a hybrid tended to produce certain definite types, and possibly in definite proportions." From this insight Spillman speculated, "While the results here reported are not sufficient to justify the positive assertion that certain quantitative laws govern the transmission of parental characters to hybrid offspring, yet they point so strongly in this direction that we may state some of these laws provisionally, looking to future investigation for their confirmation, modification, or rejection." The rules that Spillman promulgated were:

1) first-generation hybrids from a cross between two pure-breeding parents were uniform and could look like either parent or be intermediate; 2) "the types that tend to occur in the second generation . . . include all possible combinations of the characters of the two parents . . . including the parent forms themselves"; 3) "the type that is most abundant in the second generation is the same as the first generation type, whether the latter is of the usual intermediate type or otherwise."

While, as has been noted, Spillman's analysis falls short of a complete statement of Mendelism, no one reading Spillman's report today can doubt but that within a very short time he would have, following the methodology he had already developed, arrived at a complete description of the mechanism of heredity.

It would certainly appear that throughout the latter half of the nineteenth century the technique of hybridization, as applied by the practical breeders and the botanists, was gradually yielding the knowledge that was essential to the development of the science of heredity: a controlled method of crossing particular individuals of known composition; an understanding of the need to carefully count and record the different kinds of progeny from these crosses; application of the methods of statistics to describe the kinds of progeny to be expected; a recognition of the importance of chance in the transmission of traits; and especially a recognition of the potential of the technique of hybridization as a tool for understanding the process of heredity—a tool which had already made both breeders and botanists cognizant of the Mendelian phenomena of dominance, segregation and independent assortment. Moreover, had Mendel's work not been rediscovered in 1900, there were hybridists on the scene whose own experiments indicate that, in time, they too would have ferreted out the principle of segregation—such men as Spillman, Webber and Bateson. Spillman (1903) has suggested that another potential rediscoverer of Mendel's law was the plant breeder L. H. Bailey, "One reason why Mendel's law was not discovered long ago is doubtless to be found in the fact that the large majority of seedlings that have come under the breeder's eye have had heterozygote parents of unknown constitution. If all our leading commercial varieties had been commonly close-fertilized, the law would long ago have forced itself upon us. Professor Bailey's remarkable and careful work on hybrid squashes and pumpkins probably came to naught for this very reason. Had he done the same work with varieties that are normally close-fertilized, he would probably have discovered this law. He was on the right road, but he was in the wrong vehicle."

THE PATH OF THE CYTOLOGISTS

Probably the single most critical element in Mendel's (1866) study was his acceptance of the description of fertilization as "the complete union of elements from both fertilizing cells . . . . A thorough proof for complete union of the content of both cells presumably lies in the universally confirmed experience that it is immaterial to the form of the hybrid which of the parental types was the seed or pollen plant."

There was no doubt in Mendel's mind that the zygote was the product of the union of the female and male germ cells. However, this view of fertilization was not a generally accepted one in the mid-nineteenth century. For a long time, the male parent was thought to provide no material contribution to the developing egg, merely an insubstantial "aura" which was needed to activate development in the egg. Others maintained that the male germ cell only provided "contact" needed to initiate development. It was only in the latter quarter of the nineteenth century that microscopes and staining techniques were improved sufficiently to allow direct observation of the process of fertilization. The actual fusion of the male and female germ cell nuclei was first observed in 1876 (an excellent discussion of the cytological history of fertilization can be found in John Farley's book *Gametes and Spores* [1982]). Therefore, it was only in the late nineteenth century that biologists in general were convinced that the zygote was the product of the fusion of female and male gametic nuclei. This cytological achievement was of enormous significance for the origins of genetics.

The essential principle of Mendelian genetics is the law of segregation. Mendel hypothesized that to account for the ratios he observed in his hybrid progeny, paired factors must separate from each other at the time of gamete formation. However, Mendel's law of segregation called for an, as yet, undiscovered, biological mechanism. It was the research of the nineteenth century cytologists that not only provided a description of this mechanism, but also revealed the central component of the mechanism—the sine qua non of heredity—the chromosome.

In the 1870s, a deeply staining substance (designated chromatin) was discovered in the nucleus. It was observed that during the division of the nucleus, this substance appeared to break up into discrete, thread-like bodies, called chromosomes and by the last decade of the nineteenth century it was generally, although not universally, agreed that the material basis of heredity was identical with, or contained in, these chromosomes. August Weismann, in his 1892 treatise *Das Keimplasm,* summarized his views on heredity that had been developed over the years since 1876. Thus he wrote, "Both in animals and plants, however, essentially the same substance is contained in the nucleus both of the sperm cell and egg cell: —this is *the heredity substance of the species.* There can now be no longer any doubt that the view which has been held for years by Strasburger and myself is the correct one, according to which *the nuclei of the male and those of the female germ cells are essentially similar,* i.e., in any given species *they contain the same specific hereditary substance.* The splendid and important investigations carried out by Auerbach, Butschli, Flemming, . . . and by van Beneden, Boveri and others, have given us the means of ascertaining more definitely what portion of the nucleus is the substance on which heredity depends. As already remarked, this substance corresponds to the 'chromosomes,' those rod-like, looped, or granular bodies which are contained in the nucleus, and which become deeply stained by coloring matters."

E. B. Wilson, in the first, 1896, edition of his very important and influential book, *The Cell in Development and Inheritance,* summarized contemporary, mainstream opinion in the cytological tradition. He clearly agreed with Weismann that the chromosomes almost surely were the vehicles of inheritance. In support of this idea, the most compelling general evidence that he adduced was the mass of observations that showed that for almost all cells in almost all organisms, the chromosomes, and they alone among cellular constitutents, exhibited a species-specific recurrent constancy in number and in form. Moreover, this constancy was maintained by virtue of a highly organized and complex series of chromosomal and cellular maneuvers that had to be repeated during every cell division. The maintenance of a mechanism so complex implied that the resultant chromosomal constancy was a fundamental attribute of the species.

The second compelling argument for the chromosomes being, or bearing, the hereditary material was first formulated as a truly brilliant intuitive thrust by Weismann in 1885. Weismann reasoned that if, as observation suggested, fertilization was effected by a fusion of egg and sperm cell nuclei, then the resultant fusion nucleus must contain twice the amount of chromosomal material than either parent contained. Moreover, this chromosomal doubling would, of necessity, occur in every generation: an obviously untenable contention. He therefore predicted a special cell division, preceding gamete formation, during which the chromosomal content would be halved, so that at every fertilization the species-specific chromosomal constancy would be reestablished. By the end of the nineteenth century, the general occurrence of this special cell division (meiosis) was no longer doubted.

It is of interest to note that just as the hybridists had described the occurrence of dominance, segregation and independent assortment of characters without understanding the significance of these observations, so too had the cytologists described the process which led to the reduction of the hereditary material without understanding the particular maneuvers of the chromosomes which produced this reduction. If, in the period 1890–1900, cytologists generally accepted that the chromosomes were the vehicles of inheritance and that germ cells were produced by meiosis, what prevented them from recognizing meiosis as the mechanism responsible for the segregation of the chromosomes and consequently for the separation of the hereditary factors carried by the chromosomes? In other words, what prevented the cytologists from inferring the law of segregation from their observation of meiosis?

Mid-nineteenth century microscopical techniques left two lacunae in the chromosome cycle, and it was these that resulted in a fundamental misappreciation about the consequences of meiosis (Baxter and Furley, 1979). The two fundamental issues that baffled pre-rediscovery cytologists were the fate of the chromosomes between successive cell divisions, and the composition of the tetrad. Between mitotic divisions, the chromosomes elongate enormously until they can no longer be distinguished as individual chromosomes with the resolving power of the ordinary light microscope. In 1900, therefore, it was necessarily still a matter for speculation whether the chromosomes maintained their individuality throughout the cell cycle, or whether they dissolved at the end of each cell division to reform anew for the next mitosis (or meiosis).

A considerable body of indirect evidence favored continuity. The cytologists, Th. Boveri among others, had shown that chromosomes "reappeared" in sister cells in the same number, in the same shape, and even in approximately the same relative positions as they occupied when they had "disappeared" at the end of the preceding mitosis. More striking yet were Boveri's (1888) findings that whenever a chance anomaly in chromosome number or shape appeared, this anomaly was faithfully reproduced in every subsequent mitotic cell division (Sturtevant, 1965). Despite these observations suggesting chromosomal continuity, however, the chromosomes, as a matter of direct observation, appeared to dissolve so the issue could not be definitively decided.

Moreover, when the chromosomes appeared after the end of the last premeiotic mitosis in a nucleus about to undergo meiosis, the chromosomes had already doubled and very rapidly formed tetrads. Because the nature of the chromosomal reappearance was unclear to the turn-of-the-century cytologists, so inevitably was the composition of the tetrad uncertain—a matter of overwhelming importance in the present connection, because in the composition of the tetrad lay an understanding of heredity.

The cytologists were not unaware of this problem. On the contrary, to them it was a central issue. Wilson, in his 1896 treatise, makes the matter clear when he writes, "It is generally agreed that each tetrad arises by a double division of a single primary chromatin-rod. Nearly all observers agree further that the number of primary rods at their first appearance in the germinal vesicle or in the spermatocyte-nucleus *is one-half the usual number of chromosomes* . . . ." However, elsewhere, Wilson states, "When, however, we attempt a more searching analysis by considering the origin of the tetrads and the ultimate meaning of reduction, we find ourselves in a labyrinth of conflicting observations and hypotheses from which no exit has yet been discovered."

Because, then, the cytologists were, at the moment that Mendel's paper was rediscovered, uncertain about chromosomal continuity and completely in the dark about the chromosomal composition of the tetrad, despite their identification of the chromosomes as the genetic material, they were not in fact able to derive the principles of heredity solely from their observations of the chromosomes. However, it is self-evident that the problem was already sharply focused, and that observation was steadily improving; it seems overwhelmingly probable, therefore, that an understanding of the principles governing hereditary transmission would shortly have emerged from research in the microscopical tradition.

The critical microscopical breakthrough was the recognition of the role of homologous chromosomes in the composition of the meiotic tetrad. This understanding was first achieved by T. H. Montgomery in 1901, who, indeed, did not explicitly interpret his cytological findings in Mendelian terms. What Montgomery found was that, "In the synapsis stage is effected a union of paternal with maternal chromosomes, so that each bivalent chromosome (tetrad) would consist of one univalent paternal chromosome and one univalent maternal chromosome." Montgomery clearly recognized the critically important fact that meiosis must result in the separation of paternal from maternal homologous chromosomes, and in their ultimate sequestration in separate germ cells.

The first attempt to link meiosis and hereditary transmission was effected by W. A. Cannon who published his results in 1902. Cannon had shown that hybrid cotton plants which are fertile exhibited normal meiosis, whereas it was already known that sterile hybrids of *Syringa* (lilac) exhibited abnormal meiotic divisions. Cannon argued from his demonstration of meiosis in fertile hybrids that the separation of maternal from paternal factors which Mendel's law of segregation demanded could not, thus, depend upon irregularities in meiosis, and therefore the normal meiotic divisions must account for this separation. Cannon, as can be seen, postulated only a specific relationship between meiosis and Mendel's law of segregation. And even in that connection his evidence was highly inferential. Moreover, Cannon clearly appears to have imagined that at reduction all the maternally-inherited chromosomes separated from all of their paternally-inherited homologues. In this he was of course mistaken, and his speculation would have made the many observed cases of independent assortment very difficult to reconcile with chromosome behavior.

The definitive statement of the Chromosome Theory was published in 1902, 1903 by W. S. Sutton, based on Sutton's cytological work on meiosis in *Brachystola*. Sutton, working strictly cytologically, reports a careful study "of the whole division-process, including the positions of the chromosomes in the nucleus before division, the origin and formation of the spindle, the relative position of the chromosomes and the diverging centrosomes, and the point of attachment of the spindle fibers to the chromosomes." From this careful study, Sutton reached three very important conclusions (and made one misinterpretation that need not concern us here). The three important conclusions, in Sutton's words, were: "(1) The chromosome group of the presynaptic germ-cells is made up of two equivalent chromosome-series, . . . one of these is paternal and the other maternal. (2) The process of synapsis (pseudoreduction) consists in the union in pairs of the homologous members . . . . (3) The chromosomes retain a morphological individuality throughout the various cell-divisions."

In addition to these three conclusions, Sutton specifically looked into the question of whether all paternal chromosomes separate from all maternal chromosomes and concluded that "the results gave no evidence in favor of parental purity of the gametic chromosomes as a whole. On the contrary, many points were discovered which strongly indicate the position of the bivalent chromosomes in the equatorial plate of the reducing division is purely a matter of chance—that is, that any chromosome pair may lie with maternal or paternal chromatid indifferently toward either pole irrespective of the positions of other pairs . . . ."

Thus it can be seen that Sutton posited, along with cytological evidence, a complete theory of hereditary transmission that could well have been used in place of the principles of segregation and independent assortment. This formulation, moreover, would have been the end result of a long, steady development starting with the Cell Theory of Schleiden and Schwann, rather than a sudden, Mendel-like, illumination.

THE RECEPTION OF MENDEL'S WORK

By 1900, the hybridists and cytologists had accumulated enough information to allow them to ask the appropriate questions about the phenomena associated with heredity. When Mendel's paper was rediscovered, it provided the hybridists with an explanation for the previously haphazard behavior of characters in successive generations; it enabled the cytologists to "see" what chromosomes paired and how they paired during tetrad formation. It is, therefore, not a matter of overstatement to say that when Mendel's work was brought to the attention of the scientific community for the second time, its significance was immediately apprehended. W. E. Castle, in a paper entitled "Mendel's Law of Heredity" (1902), dubbed Mendel's theory "one of the great discoveries in biology and in the study of heredity perhaps the greatest." Spillman (1903) declared, "No discovery in recent years has aroused more interest amongst biologists than that of Mendel's Law. If subsequent investigations confirm it, as those thus far may have done, it can not be considered less than epoch-making . . . . It is impossible, on the threshold of such a discovery to state just how far-reaching its importance is; we must wait for further investigation before hoping for too much."

A glimpse at just how well primed biologists were to receive and make use of Mendel's laws is evident from the second report given by Bateson to the Evolution Committee of the Royal Society (1905), in which Bateson remarked, "During the two years that have passed since the publication of Report I the growth of Mendelian literature has been so rapid that it is impossible to give any adequate summary here." Indeed, by 1913, Bateson in his treatise, *Mendel's Principles of Heredity*, was able to list 27 genera of plants and over 21 genera of animals—ranging from man and other mammals through a mollusk—in which Mendelian genes specifically for color differences had been demonstrated. It is startling to realize the degree of sophistication achieved with the application of Mendel's laws. Already in 1902 Garrod and Bateson had presented evidence that the disease alcaptonuria was caused by a recessive gene, in man. Further work by Garrod led to the publication of his book *Inborn Errors of Metabolism* (1909) in which he showed that alcaptonuria and several other "Mendelizing" diseases of man were caused by the absence of a specific enzyme. Garrod had, in fact, postulated the relationship between gene and enzyme.

Already "geneticists" were beginning to expand the application of the Mendelian laws and the Mendelian methodology to instances other than the 3:1 or 9:3:3:1 ratios. Investigations into the study of multiple alleles and multiple genes followed suit. Moreover, geneticists had become so sure of their techniques of analysis and so confident of the operation of the laws of segregation and independent assortment, that the discovery of the linkage of factors, a principle not mentioned by Mendel, was easily accommodated. Ten years into the twentieth century saw the establishment of a "new" discipline which beckoned its practitioners with the promise of discoveries as yet undreamed, with the potential for knowledge as yet unplumbed.

THE LOGIC OF MENDELIAN GENETICS

The logical unity of the Mendelian system, the fact that the entire explanation of the transmission of hereditary traits from one generation to the next flows from but a single basic proposition—the principle of segregation—and a small number of auxiliary observations, suggests that the understanding of Mendelism must come all at once or not at all, and must, of necessity, take the form that is so familiar to us. So indeed it was discovered by Mendel himself, so it was asserted to have been rediscovered by all three rediscoverers, and so it is to this day treated in virtually every textbook of Genetics.

The detailed study of the rediscovery and of biology at the turn of the century presented here, however, suggests quite strongly that such a view is mistaken. In the first place we have seen that the identity of the treatments by Mendel and the rediscoverers was primarily a consequence of the power of Mendel's conceptualization and was not in fact a number of independent investigations that led to the same formulation. Moreover, and more compellingly, we have seen that many other turn of the century breeders, most strikingly, W. S. Spillman, had seen parts of the solution to the problem of hereditary transmission and had formulated answers quite differently from the way Mendel had. It seems clear that had Mendel not worked, or had his paper not been rediscovered (or, indeed, been rediscovered some years later than in fact it was), an understanding of the principles of heredity could well have developed in a slower, more piecemeal fashion.

In fact, it seems reasonably likely that even had the whole school of plant hybridizers not succeeded in properly interpreting heredity, a solution to that problem would have emerged in the years around 1900 from the cytological work on cells and subcellular organelles. Thus, in 1903, when Sutton made the causal relationship between the behavior of the chromosomes and the behavior of the Mendelian genes explicit, he asserted that he had arrived at his understanding of the behavior of the chromosomes in heredity prior to his having read Mendel's paper. "The general conceptions here advanced were," Sutton wrote, "evolved purely from cytological data, before the author had knowledge of the Mendelian principles . . . ." There seems no reason to doubt his assertion, and from these "general conceptions" to Mendel's laws was not far to go.

Moreover, Sutton was not alone in this approach. On the contrary, almost immediately following the rediscovery of Mendel's principles, several different workers (Bateson, Boveri, Wilson and Cannon) all, independently, noticed the equivalence between Mendel's laws and the behavior of the chromosomes during meiosis. It seems clear, therefore, that the cytologists would have, on their own, shortly arrived at a solution to the mystery of heredity—a solution, however, that would have been framed in terms of chromosome behavior with genetic results (the principle of segregation and the resultant progeny ratios) noticed only as corollaries.

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The Structure and Organization of Genetic Material[1]

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SYNOPSIS. Some of the major features of nucleic acid structure and replication are reviewed in respect to their constancy and variability. These two qualities of conservation and change are broadly discussed in terms of the roles that genetic informational molecules play in biological evolution.

INTRODUCTION

There are perhaps two approaches in teaching the structure of genetic material as a process of discovery; that is, in exploring this topic in the context of our symposium, "Science as a Way of Knowing." One approach, that of describing why and how genetic material was historically discovered by biologists, has already been partially provided for you by Dr. Moore in the essay that accompanies this symposium, and is further discussed in various genetics textbooks, and in the more thorough accounts of Judson (1978), Olby (1974), Portugal and Cohen (1978), Watson (1968), and many others. The second approach, to try to understand and explore the role that genetic material occupies in biology because of evolutionary changes in its structure and organization, can be as interesting for some students as the more historical approach, and is one to which this paper is mostly devoted.

The cornerstone of this discussion is that genetic material provides to all of biology two basic qualities that enable evolutionary changes to occur: *constancy* and *variability*. Constancy provides the basis for our fundamental genetic observation that "like produces like," and variability provides the basis for change in the sense that "like also produces unlike." If we define evolution as changes in biological information over time, it is clear that evolution must entail changes (variability) in the duplication (constancy) of biological information. Since both of these qualities derive from the processes by which genetic material is copied and transmitted, we can begin with briefly examining the molecular structure of this material and its mode of replication.

The genetic material of all terrestrial organisms dating back to the early history of life, four billion or so years ago, has probably been primarily, if not entirely, in the form of nucleic acids (Fig. 1). These are long-chained molecules composed of nucleotide subunits, each containing a pentose (5-carbon) sugar, a monophosphate group, and a nitrogenous base. The two kinds of sugar used in nucleic acids, ribose (hydroxylated at the 2′ carbon position) and deoxyribose (lacks 2′ hydroxyl) provide the names for the two kinds of nucleic acids, ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). The phosphate groups occupy the same position in both nucleic acids, serving to tie the 3′ carbon of one sugar to the 5′ carbon of its neighbor via a phosphodiester bond. Connected to the 1′ carbon of each sugar is one of four kinds of nitrogenous heterocyclic bases, two of which are purines (adenine [A] and guanine [G] in both DNA and RNA) and two are pyrimidines (cytosine [C] and thymine [T] in DNA, and cytosine [C] and uracil [U] in RNA).

It would seem that the restriction of nucleic acid composition to only four different kinds of bases would limit the message-bearing capacity of these molecules to only four kinds of messages; but this is, of course, not so. The fact that nucleic acid molecules may be many thousands or millions of nucleotides long, and that each message can be encoded by a unique linear sequence of nucleotides, endows these molecules with the capacity to bear an

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[1] From the Symposium on *Science as a Way of Knowing—Genetics* presented at the Annual Meeting of the American Society of Zoologists, 27–30 December 1985, at Baltimore, Maryland.

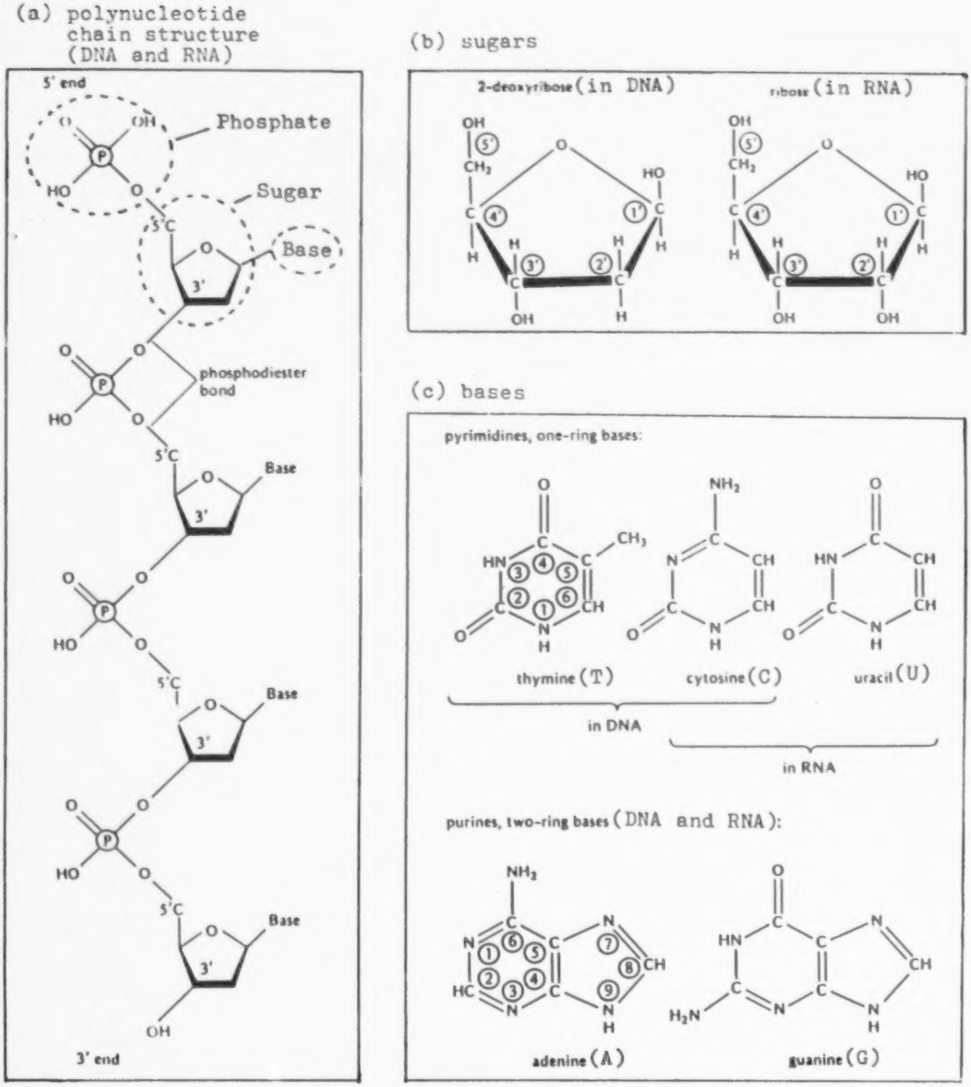

FIG. 1. Structural formulae for nucleic acids and their components. (a) Structure of a tetranucleotide sequence showing the general positioning within a nucleotide of the phosphate group, the sugar moiety, and the nitrogenous base, as well as the phosphodiester bonds that connect nucleotides together. (b) The two kinds of sugars found in cellular nucleic acids. (c) The common bases and their designations.

immense variety of immensely complex messages. For any one nucleotide position, 4 different messages are possible (A, G, C, or T); for two nucleotides in tandem, 16 different messages are possible (AA, AG, AC, AT, GG, GC, . . .); and so on: the rule being simply that for a linear sequence of *n* nucleotides, 4^n different possible messages can be encoded. Thus a linear sequence of only 10 nucleotides can be used to discriminate between more than one million potentially different messages.

In reality the biological messages that nucleic acids carry are mostly translated

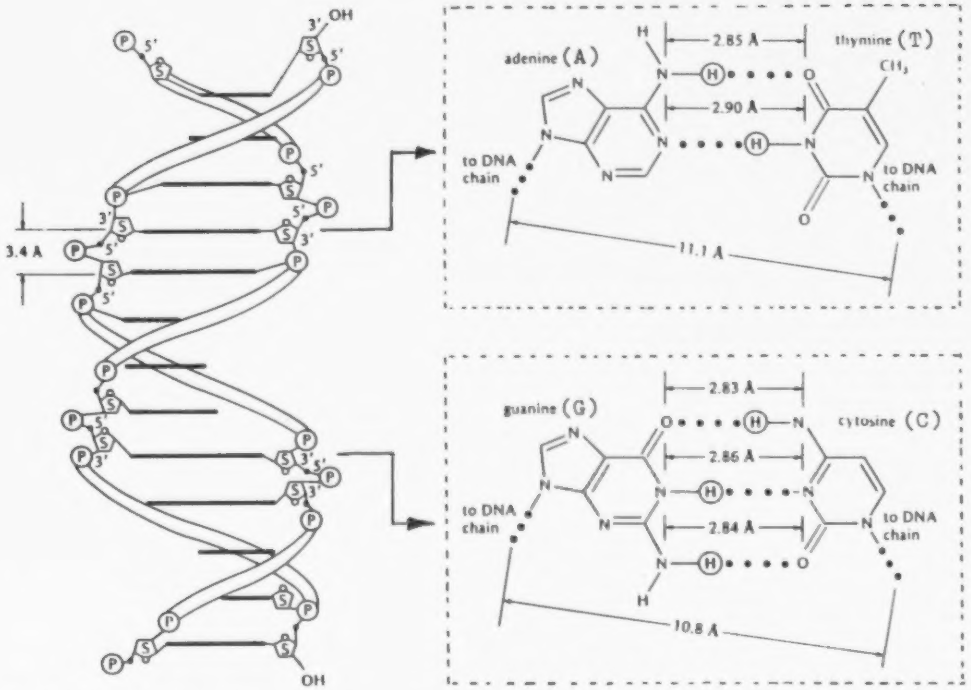

FIG. 2. The Watson-Crick model of the common B form of the DNA double helix. Some of the individual phosphates (P) and deoxyribose sugars (S) are drawn in each strand to indicate the opposite orientations of the two strands. Also indicated are the complementary base-pairing relationships between the strands because of hydrogen bonding between adenine-thymine and between guanine-cytosine. (After Strickberger, 1985.)

into proteins, composed of linear chains of amino acids (polypeptides). Since 20 different kinds of amino acids are used in this translation, there is a minimum, as well as actual, sequence of three nucleotides necessary to code for any one of these amino acids and for protein termination signals. These triplet nucleotide sequences comprise the 64 different "codons" in the present genetic code, and can be arranged in various ways and in various lengths to provide all the many possible kinds of organismic proteins that may ever have existed, beginning with that early stage in which this code was first established.

All of this helps explain the information-carrying role of nucleic acids but does not explain how this information is replicated and transmitted. The model presently accepted for nucleic acid replication is, as we know, derived from the now-familiar double helix structure first offered by Watson and Crick (1953). The DNA double helix is composed of two antiparallel strands coiled around each other in the form of a right-handed screw, with complementary pairing between purine bases on one strand and pyrimidine bases on the other (A-T, G-C). In the familiar "B" form of DNA, diagrammed in Figure 2, there are approximately 10 base pairs for each complete turn of the helix, and the bases are stacked almost perpendicularly to the helical axis. In the "A" form, 11 bases are reported per turn of the helix, and the bases are noticeably tilted (20°) relative to the helical axis. The characteristics of these two forms as well as those of other right-handed DNA double helices (C, D, and E) are correlated with relative humidity, salt concentration, ionic strength, and solvent polarity. Changes in these molecular environments apparently cause changes in the planar arrangement ("puckering") of sugar atoms

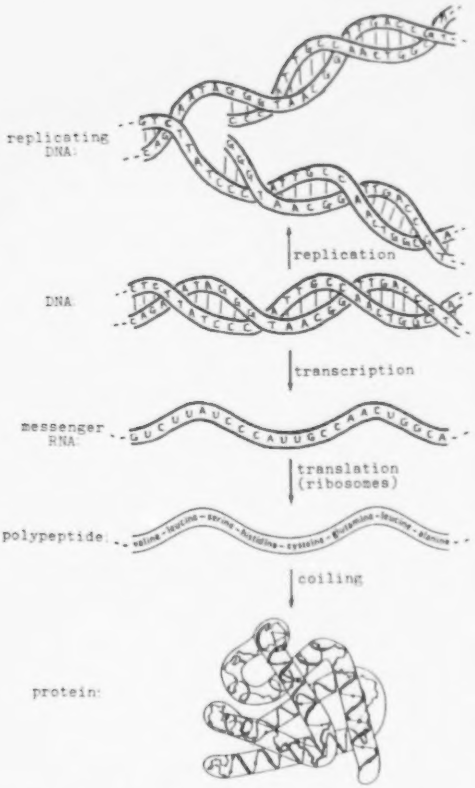

FIG. 3. Diagram of how sequential information is transferred between the three major biomolecular polymers, DNA, RNA, and protein. Among the cellular choices are to replicate a DNA molecule by means of DNA polymerase enzymes to produce two identical double strands, or to transcribe one strand of a DNA molecule into RNA by means of RNA polymerase enzymes. Transcribed RNA can then act as a "messenger" which is translated by ribosomal machinery into a polypeptide chain that then folds to form a protein or protein component. The nucleotide sequence on messenger RNA is exactly complementary to its DNA template, and a triplet of three nucleotides (triplet codon) on the messenger specifies one amino acid.

in the DNA backbone, and changes in distance between adjacent phosphate groups, which then, in turn, modify the nucleic acid helical conformation (see Saenger, 1984).

The replicatory power of the DNA double helix obviously derives from the ability of each of the two strands to serve as a template for a newly complementary strand, so that two new double helices can be formed bearing nucleotide sequences that are identical to each other and to that of the parental molecule (Fig. 3). For myself and many others, it was Meselson and Stahl's (1958) experimental support for such "semiconservative" replication that brought the Watson-Crick DNA model past the stage of being merely a very attractive hypothesis.

To briefly summarize so far, the structure of nucleic acids encodes information by means of the linear placement of four different kinds of nucleotides. This information can be replicated via polymerase enzymes; and can be used biologically, mostly by translation into polypeptides. In cells, sequential information in DNA is transmitted to other cells by replication, thus providing the "genotype." The expression of this information, the "phenotype," begins primarily with the transcription of this sequential information into the various kinds of RNA (messenger, ribosomal, transfer), followed by the subsequent translation of messenger RNA into amino acid sequences, and then by all of the various interactions that characterize the organism.

THE PERENNIAL "GOLDEN AGE"

This one-way direction for transfer of molecular sequential information, nucleic acid to protein, prompted Crick (1958) to depict this as the "Central Dogma," and it seemed as though an understanding of all basic genetic molecular features would soon be at hand. In fact, within a decade, by the late 1960s, some molecular biologists suggested that the "Golden Age" of progress in biology was coming to an end, and there were probably very few real surprises in store (Stent, 1969). Nevertheless, depending on how easily one is surprised, investigations into the structure of genetic material continue to offer unforeseen novelties which help to provide an appreciation of how extensive are both the variability and the change experienced by these basic molecules. Among such "surprises," have been the following:

1. The discovery that the transmission of sequential information occurs not only in the direction of DNA → RNA, but also

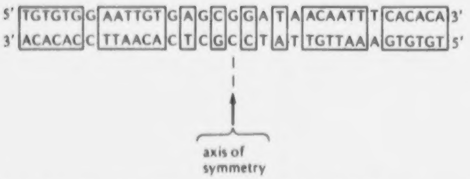
5' TGTGTG G AATTGT G A G C G G A T A ACAATT T CACACA 3'
3' ACACAC C TTAACA C T C G C C T A T TGTTAA A GTGTGT 5'
axis of symmetry

FIG. 4. Nucleotide sequence of the *E. coli* operator region at which the *lac* repressor attaches that controls the synthesis of enzymes involved in lactose metabolism. The symmetry of this region is "palindromic" because the sequences in the boxes to the left of the axis of symmetry are inverted repeats of the boxes to the right of this axis. (After Strickberger, 1985.)

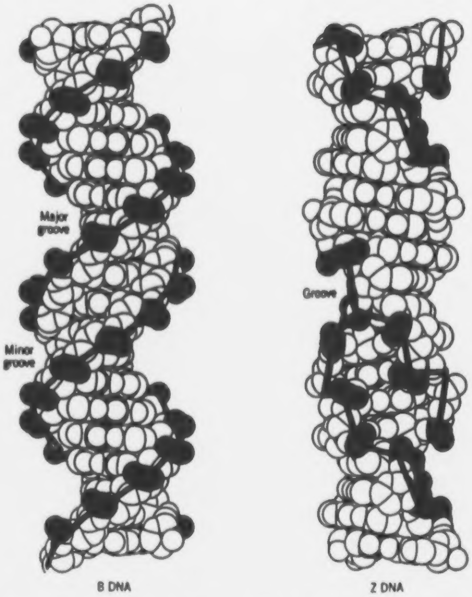

FIG. 5. Space-filling models of B-DNA and Z-DNA double helical molecules. The heavy lines used to connect the phosphate groups in each chain show the zigzag placement of phosphates in Z-DNA in contrast to the smoother curve of their relationship in B-DNA. The "major" and "minor" grooves in B-DNA differ in depth but do not extend to the central axis of the molecule, whereas the indicated Z-DNA groove penetrates the axis of the double helix. (After Rich *et al.*, 1984.)

in the direction RNA → DNA. Such "reverse transcription," catalyzed by the enzyme reverse transcriptase, is the mode by which RNA retroviruses incorporate their genetic material into the DNA of host chromosomes (see, for example, Weiss *et al.*, 1982).

2. The discovery that DNA sequences carry not only information expressed through transcription and translation, but also information that determines the conformation of the molecule itself. For example, "palindromic" sequences which present the same nucleotides (but with inverted order) on either side of a central axis are used in some genes as part of the recognition sites ("promoters") for enzyme attachments that help initiate transcription, or used as sites for the attachment of repressors that prevent transcription (Fig. 4). These and other special DNA sequences such as "inverted repeats" can produce loops, twists, and kinks that allow interaction between DNA and various enzymes, viruses, and plasmids, and also provide loci at which mutation rates are preferentially increased or decreased (see, for example, Miller, 1983). In eukaryotes, DNA is organized into nucleosomal structures using histone proteins, and specific nucleotide sequences undoubtedly also play a role as recognition sites that help activate nucleosome placements or displacements (see Eissenberg *et al.*, 1985).

3. The discovery that DNA may be coiled in a left-handed rather than right-handed direction (Fig. 5). Such left-handed double helical sections, called "Z-DNA" because of their zig-zag placement of phosphate groups, were first associated with alternating CG sequences but are now also observed in other sequences as well. Like some other distortions of the DNA molecule, Z-DNA is believed to occur within particular chromosomal regions at which regulatory activity takes place (Rich *et al.*, 1984).

4. The discovery of DNA sequences in eukaryotes that are repeated many times over (Table 1). Some of these repeated sequences are very short, and are localized to specific chromosomal regions such as centromeres, whereas others of somewhat longer lengths are dispersed throughout the genome. In mammals, among several families of dispersed sequences that have been identified, is the *Alu* family found in primates, represented by perhaps more

TABLE 1. *Estimates of the frequencies of nonrepetitive DNA sequences and three classes of repetitive DNA sequences in various genomes.*

Organism	Nonrepetitive (single copy)	Partially repetitive (to about 200 copies per genome)	Intermediate repetitive (250–60,000 copies per genome)	Highly repetitive (70,000–1,000,000 or more copies per genome)
Chlamydomonas reinhardtii (algae)	0.70		0.30	
Physarum polycephalum (fungus)	0.58		0.42	
Ascaris lumbricoides (annelid)	0.77		0.23	
Drosophila melanogaster (fruit fly)	0.78	0.15	0.07	
Strongylocentratus purpuratus (sea urchin)	0.38	0.25	0.34	0.03
Xenopus laevis (clawed toad)	0.54	0.06	0.37	0.03
Gallus domesticus (chicken)	0.70	0.24		0.06
Bos taurus (cattle)	0.55		0.38	0.05
Homo sapiens (human)	0.64	0.13	0.12	0.10

Compiled from data in Straus (1976).

than one million copies per human diploid cell (Jelinek and Schmid, 1982). The evolutionary origin of prolific sequences of this kind appears to be related to their possession of promoter regions that enable attachment of RNA polymerase (pol III) enzymes that would ordinarily transcribe transfer RNA genes. It is possible and perhaps even likely that transcription of such sequences into RNA can be followed by their reverse transcription into DNA, and their subsequent incorporation into host chromosomes in a manner similar to retroviruses. In support of this view are findings indicating that the sequences of some *Alu*-like families are obviously derived from transfer RNA genes, and such repeats also possess certain sequences that may be necessary for recognition by reverse transcriptase (Rogers, 1985).

5. The discovery of mobile "transposable" DNA elements that can shift their position to various parts of the genome during the period of observation. Their presence was initially demonstrated by Barbara McClintock (1951) in maize, and they have since been shown to be prevalent in prokaryotes as well as eukaryotes. They can account for the interspecific transfer of various traits including antibiotic resistance factors in bacteria, and thereby provide means for the "horizontal" transmission of genetic information (Syvanen, 1984). However, like some of the repeated DNA sequences mentioned above, it is apparent that many of these transposable elements may contribute very little, if any, function to the host, and they have therefore been termed "selfish DNA."[2]

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[2] Although "selfishness" indicates that a unit of life is primarily concerned with its own replication, I believe it debatable whether, as argued by Dawkins (1976), such selfishness is the exclusive property of DNA simply because it replicates itself so well, and organisms are therefore to be considered merely the means for the replication of DNA. Attempts to reduce explanations of life to such very simple levels can lead easily to a rather meaningless chain of arguments: organisms are the means enabling cells to replicate; cells are the means enabling chromosomes to replicate; chromosomes are the means enabling genes to replicate; genes are the means enabling codon replication; codons are the means enabling nucleotide replication; nucleotides are the means enabling the replication of nitrogenous bases, sugars, phosphates, etc., until statements can be developed affirming that all organisms are the means enabling the perpetuation of various atomic or even subatomic particles. It would seem that "selfishness" may have some meaning in terms of one component of life competing with similar components at the same level of organization ("selfish" organisms, "selfish" cells, "selfish" DNA, etc.), but there is little understanding to be gained by trying to establish which level is most selfish.

6. The discovery of "split" eukaryotic genes in which amino acid-coding nucleotide sequences called "exons" are interrupted by noncoding sequences called "introns" (Fig. 6). The sequences in these split genes are transcribed from DNA to RNA, and the RNA is then "processed" so that the introns are removed and the exons spliced together. Such processed mature messenger RNA molecules are then transported across the nuclear membrane to the cytoplasm to be translated into polypeptides. Whatever the advantages of intron-exon structures, these seem sufficiently great to account for the fact that gene splitting occurs in almost all vertebrate protein-coding genes so far examined, as well as in many similar genes in other eukaryotes. Gilbert (1979) suggested that each exon may have originally coded for a single polypeptide "domain" that could be used for a specific function, and others such as Blake (1985) suggested a relationship between the average size of an exon (coding for about 20 to 80 amino acids) and the size of the smallest polypeptide sequence that could be folded into a stable structure (about 20 to 40 amino acids). Because of the flexibility of exon arrangement and intron removal, the exons coding for these polypeptide subunits could then be combined in various ways to form genes that produced optimal polypeptides. According to Doolittle (1978) and others, cellular organisms ancestral to both prokaryotes and eukaryotes possessed such intron-exon structures, but these were abandoned in prokaryotic lines because of an increased intensity of selection for "streamlining" DNA replication and transcription efficiency.[5]

7. The discovery of "pseudogenes," defined as nucleotide sequences that are inexact nonfunctional copies of normally active genes (Li, 1983). Pseudogene nonfunctional status may be caused by one or more mutations that affect transcription (mutated promoters), RNA processing (mutated introns), or translation (nonsense mutations). It was also surprising to find that all introns had been removed from some pseudogenes ("processed genes"), indicating that they had been incorporated into DNA by the reverse transcription of previously processed messenger RNA molecules. In many instances, pseudogenes are found closely associated with their active gene counterparts in "gene clusters," thus helping to provide evidence for the prevalence of mechanisms such as unequal recombination which is believed to have produced many genes and gene families by duplication.

8. The discovery that a single DNA sequence could be used to code for more than one kind of protein; that is, the existence of "overlapping genes." Overlaps of this kind may arise from the use of different translation initiation sites located along the same set of codons ("same reading frame"), or by using different sets of codons for the same nucleotide sequence ("different reading frames"). In many small genomes such as bacteriophage ϕX174 (Godson *et al.*, 1978), such overlapping genes seem to serve the purpose of increasing the number of different kinds of polypeptide products from an evolutionarily restricted length of DNA.

9. The discovery that new combinations can be formed between fairly widely dispersed DNA sequences within vertebrate

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[5] It is not clear why selection for "streamlining" should affect prokaryotes more than eukaryotes, especially since there are (and were) many single-celled eukaryotes (and even multicellular organisms) in which "streamlined" metabolic and reproductive mechanisms would be as adaptive as in single-celled prokaryotes. An alternative explanation for eukaryotic introns may lie in the necessity for messenger RNA transport across the nuclear membrane, and the role that some of the small nuclear ribonucleoprotein particles (snRNP) play in both intron excision and messenger RNA transport. Perhaps eukaryotic cells became reliant on both these functions of snRNPs once nuclear membranes had evolved and messenger RNA molecules had to be carried into the cytoplasm. Certainly, the ubiquitousness of introns in eukaryotic genes, the considerable expense in maintaining these split arrangements, and their absence in nontranslated "processed pseudogenes" (see below), indicates a function for introns beyond that of merely separating polypeptide domains that no longer need to be separated. A different explanation offered by Cech (1985) is that introns may persist because their excision from DNA molecules is rarely, if ever, exact, and they must therefore be kept intact to prevent the mis-splicing of exons. Thus intron DNA is primarily preserved because it must be transcribed into "selfish RNA"!

somatic cells to form unique antibody-producing genes. This mechanism is a somewhat different evolutionary answer to the problem described above for increasing the number of proteins in smaller genomes. In this case, selection from an array of many millions of different possible kinds of antibody proteins can occur on demand produced by only a limited number of DNA sequences (Honjo and Habu, 1985).

10. The discovery that genes can directly modify the DNA sequences of other genes within the same genome. Whereas normal recombinational mechanisms that account for the exchange of sequences between homologous chromosomes are usually performed reciprocally (*e.g.*, *ABC* × *abc* → *ABc* + *abC*), a significant number of events have been identified that can only be explained as the result of nonreciprocal exchange (*e.g.*, *ABC* × *abc* → *ABc* + *aBC*). That is, a DNA sequence on a donor gene is directly adopted by a recipient gene without any modification of the donor. Such instances have been subsumed under the titles "gene conversion" (Nagylaki and Petes, 1982), "concerted evolution" (Arnheim, 1983), and "molecular drive" (Dover, 1982), and seem to result from variations in replication and recombination mechanisms. They help to explain the fact that certain repetitive DNA sequences are remarkably alike within a species, but can show significant differences between species. Apparently, these devices can "homogenize" some repetitive sequences within species so they resemble only one such sequence.

NUCLEIC ACID EVOLUTION

In addition to the more classical mechanisms of genetic change (*e.g.*, base substitutions, deletions, duplications, inversions, insertions, etc.), the various further com-

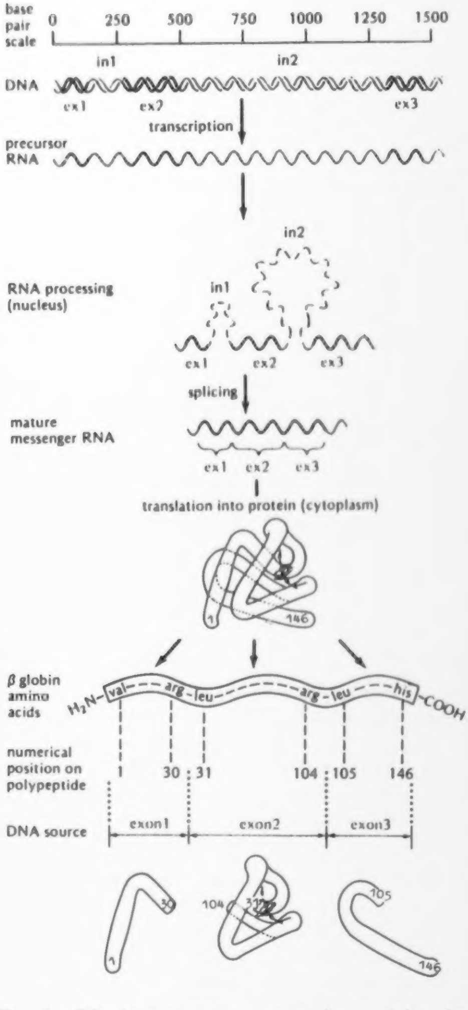

FIG. 6. The intron-exon structure for nucleic acid sequences involved in the production of the human β-globin polypeptide chain, 146 amino acids long, one of the components of normal adult hemoglobin. The top portion of the diagram indicates the approximate 1,500 nucleotide base-pair length in the β-globin DNA sequence, and the structure of this sequence in terms of two introns (in1, in2) and three exons (ex1, ex2, ex3). Intron 1 is 130 nucleotides long, and separates codons that will later be translated into amino acids numbered 30 and 31 on the β-globin chain. Intron 2, 850 nucleotides long, separates codons for β-globin amino acids numbered 104 and 105. Although the entire DNA sequence is transcribed into messenger RNA, the introns are precisely removed by special RNA processing in the nucleus, and the exon sequences are spliced together and then translated

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←

into a continuous β-globin amino acid sequence. At the bottom of this figure, a single β-globin polypeptide chain has been diagrammatically split to indicate the three subcomponents ("domains") respectively produced by the three exon nucleotide sequences. (From Strickberger, 1985, with additions.)

plexities in structure and behavior of genetic material listed above point to the immense variability that can be incorporated into these basic molecules of biological information. At the same time, because of the constancy of replication, many of these components of variability are also carried forth to further generations so that DNA can properly be considered a "historical" molecule. Its history is embedded in its nucleotide order, and comparisons between DNA molecules and sequences are now furnishing large amounts of basic data for determining evolutionary relationships (see, for example, Brown, 1983). However, one question that continually arises is whether we can determine the functional history of DNA itself: At what point did DNA become genetic material, and how did this happen?

Unfortunately, the origin of nucleic acid molecules as carriers of biological information is well hidden in the past, and ideas offered so far have been mainly conjectural. It nevertheless seems fairly certain that prebiotic conditions could have produced purine and pyrimidine bases, as well as various kinds of nucleotide structures (Miller and Orgel, 1974). A large literature on prebiotic chemical evolution has been accumulating in journals such as *Origins of Life, BioSystems, Journal of Molecular Evolution,* and others. For example, recent studies indicate that the polymerization of possible "primitive" nucleotide-like molecules can occur under prebiotic conditions where templates may either have been present or absent (Schwartz and Orgel, 1985).

Also interesting are experiments showing that selection can occur for optimal lengths among nucleic acids as well as for special nucleotide sequences that can be recognized by replication enzymes. Using the RNA nucleic acid of $Q\beta$ bacteriophage, Spiegelman and co-workers (see Mills *et al.*, 1973) showed that independent self-replicating RNA molecules can be selected in an incubating mixture that contains the $Q\beta$ replicase enzyme (RNA-directed RNA polymerase), nucleoside triphosphates, and necessary buffers and salts. Beginning with the $Q\beta$ genome, somewhat more than 4,000 RNA nucleotides long, selection for rapid replication in such mixtures led to survival of a mutant sequence called "midivariant" whose length had been reduced to only about 220 nucleotides long (Fig. 7)!

Eigen and his group then showed that when these experiments were reversed—that is, when such mixtures begin without any $Q\beta$ RNA sequences at all—the $Q\beta$ replicase will nevertheless splice together nucleotides on its own without a template. Moreover, evolution in such mixtures can produce a variety of "de novo" RNA sequences capable of adapting to different environmental conditions, including sequences that reach by accretion that optimal self-replicating "midivariant" length of 220 nucleotides! These and other experiments have led Eigen and co-workers to conclude that the number of nucleotides ("information content") in an RNA strand determines the frequency at which mutant sequences arise, as well as the number of reproductive cycles necessary for the selection of an optimal mutant with high reproductive rate (see the review by Eigen, 1983). The prevailing ("wild type") genotype achieves stability when its selective advantage is sufficiently great to overcome the error rate of replication for that nucleotide sequence. If the error rate is too high then adaptive information is lost. If the error rate is too low then the capacity for further adaptation is reduced. Such factors therefore govern the nucleotide length of a molecule in these experiments. For example, Eigen points out that since RNA polymerases do not replicate nucleotides as accurately as DNA polymerases, the RNA molecules in single-stranded RNA viruses are usually no longer than 10^4 nucleotides, a value that can be theoretically calculated from error rates and selective advantages.

One suggested scenario for the evolution of genetic material is that the replication of nucleic acids, however it first occurred, led quickly to the formation of "master" nucleic acid molecules that could be both stored and replicated. At the same time, protein synthesis had evolved to the point that such sequences could also be translated into amino acids or produce

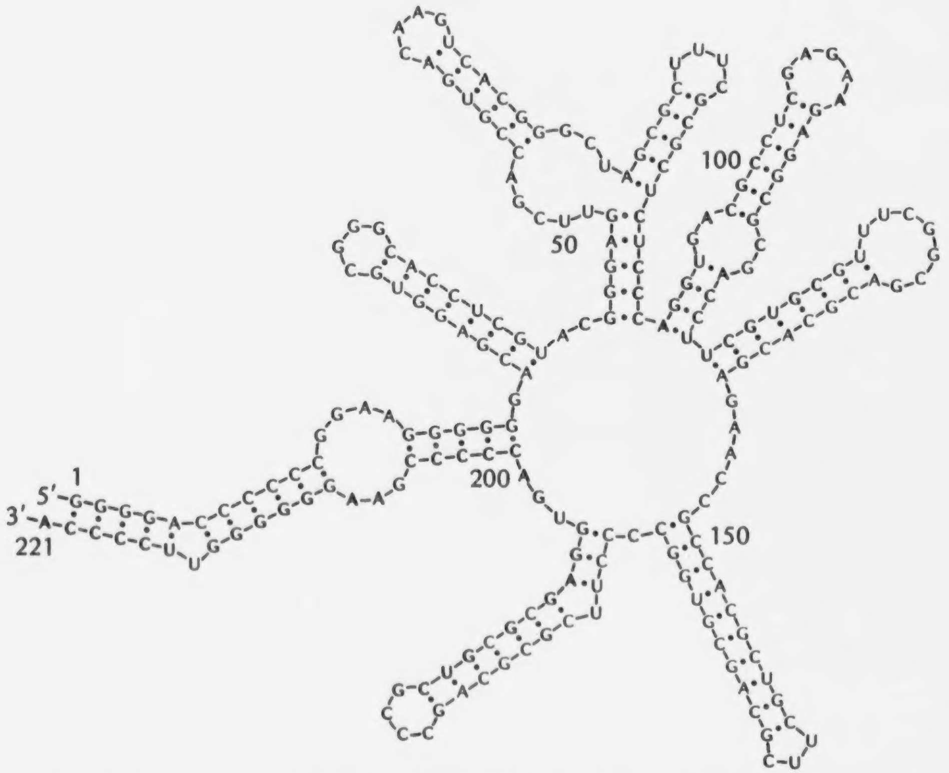

FIG. 7. Nucleotide sequence and secondary structure of the "midivariant-1" RNA molecule found after selection for rapid replication among $Q\beta$ genomes in mixtures in which RNA replicase enzymes are provided. About 95 percent of the $Q\beta$ genome has been eliminated because of this selection, and the remaining 221 nucleotides of midivariant-1 are apparently only those necessary to enable the replicase enzyme to bind to the molecule so that replication can occur. (After Miele *et al.*, 1983.)

complementary "messenger" strands for this purpose. Three separate functional classes of nucleotide sequences thus eventually arose, storage, messenger, and translational (ribosomal and transfer). These were all probably RNA, since this nucleic acid is still used for two of these purposes in all organisms (messenger and translational), and is also used for genetic storage purposes in some viruses that replicate their genetic material directly by means of RNA replicases. In addition, some RNA molecules such as transfer RNA and RNAs used in RNA processing still preserve catalytic properties, indicating that this nucleic acid may well have provided both information and some enzyme-like activity.

Cellular difficulties caused by attempting to maintain RNA molecules with two primitive but quite different functions, information storage and protein translation, would have offered advantages to organisms that could utilize a different nucleic acid for storage purposes, DNA. The enzymes that translate RNA into protein do not function with DNA, thus permitting the more uniformly structured double-helical DNA to be restricted exclusively to the storage of information and to the transcription of one of its strands to form messenger RNA. It has also been proposed that DNA genetic material would offer a more easily protected molecule than RNA because the 2′ hydroxyl group in the ribose sugar of RNA causes it to undergo more rapid hydrolytic cleavage than the 2′ deoxyribose of DNA. A third suggested reason for a change in genetic mterial is that RNA replication is more error-prone than DNA replication because RNA polymerases do not possess the exonuclease editing functions of DNA polymerase. Furthermore, the transition from RNA to DNA as the genetic material may have simply entailed the presence of reverse transcriptase enzymes. These enzymes, perhaps originally involved only in RNA replication, could later have been used to transfer genetic information from RNA to DNA.

CONCLUDING REMARKS

From everything discussed so far, I believe it is clear that the basic biological and evolutionary qualities of constancy and variability derive ultimately from the replication process utilized by nucleic acids. Faithful replication of nucleotide sequences has provided constancy, and errors and changes in nucleic acid replication have provided variability. However, although nucleic acids are essential to biological processes, it is also important to recognize that replication includes further higher orders of biological organization, in the sense that organisms, populations, and communities possess various nonmolecular qualities that are also replicated, such as sexual, social, and cultural behaviors, geographical and ecological distributions, populational and species interactions, etc.

In the selection of a balance between constancy and variability at all levels, we can see that living processes deal with the present and the future by making use of a rather remarkable hindsight. That is, although organisms have no way of predicting the exact future, they have, through their evolutionary experience, visualized the past. To the extent that the past provides a reasonable picture of the future (even past uncertainties become a picture of future uncertainties), evolution can be said to have provided informational vision that can often dimly see the future. The fact that biological processes have survived for so long is certainly testimony to the foresight provided by historical genetic information.

On the whole, it seems both valid and valuable to look at life as a series of processes rather than as one or more material entities. Certainly the preservation of life is not through the immortality of its components, since all living organisms and their organic components eventually "die." Rather, life is preserved in the sense that the information that allows living processes to persist is continually replaced by replication. It is this information, borne by genetic material and embodied in all of its many interactions, that carries with it the important biological features of constancy and variability.

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The Function of the Hereditary Materials: Biological Catalyses Reflect the Cell's Evolutionary History[1,2]

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SYNOPSIS. The recent discovery of specialized RNA molecules that function like enzymes suggests that cells evolved before there were proteins. Such RNA-based cells would have contained large numbers of mutually supportive RNA molecules, each with a different catalytic function. Protein synthesis probably evolved later and was catalyzed by some of these RNA molecules. Because DNA must have been a relatively late addition to the cell, it is reasonable to assume that all DNA functions evolved in the presence of powerful protein catalysts.

The above evolutionary perspective helps to explain why two different classes of catalytic mechanisms are used in present-day cells. The ancient processes of protein synthesis and pre-mRNA splicing are catalyzed by ribonucleoprotein particles, in which RNA catalysis still seems to play an important role. In contrast, late-evolving functions like DNA replication are catalyzed by efficient protein machines. By analogy, protein machines are also likely to mediate the processes that control the transcription of eucaryotic genes.

INTRODUCTION

The topic that John Moore assigned me for this article, "the function of the hereditary materials," is not only a broad one, but one about which we have an enormous amount of knowledge. Fortunately, however, I have been asked to try to present a fresh view here, rather than to summarize facts that are already well explained in textbooks (see, for example, Stent, 1971; Watson, 1976; Alberts *et al.*, 1983; Lewin, 1985). I have therefore decided to discuss the hereditary materials from a particular evolutionary perspective that I have found useful in thinking about the cell. As for all evolutionary analyses, the discussion can only be speculative, but I believe that the major ideas presented generate enough predictions about how cells function to be testable as we learn more details about their mechanisms.

In its most general terms, a cell is nothing more (or less) than a highly elaborate set of self-reproducing chemical reactions, and it therefore relies upon a large set of highly specific catalysts for its existence. In all of the cells we know, these catalysts are encoded by a DNA genome. As an overview of the argument to be pursued in this article, this DNA can be thought of as specifying two different families of catalysts, arbitrarily designated here as class I and class II, that derive from two very different epochs in the cell's evolutionary history (Fig. 1). The class II catalysts are the major type, being the enzymes that fill biochemistry textbooks; each is a protein molecule with an elaborately-folded catalytic surface. But at one time early in cell evolution there were no proteins as we know them, and it seems likely that the cell had to survive with RNA molecules as its major catalysts. The remnants of these early RNA-based reactions that survive constitute the class I reactions. Class I reactions can be recognized because they are catalyzed by ribonucleoprotein complexes, in which catalysis by RNA molecules still plays a significant role. These reactions are relatively complicated and unwieldy compared to class II reactions, which are often catalyzed by highly-efficient protein machines.

THE CENTRAL DOGMA IS MISLEADING

In any discussion of the hereditary materials, it is customary to start with the central dogma: DNA → RNA → protein.

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[1] From the Symposium on *Science as a Way of Knowing—Genetics* presented at the Annual Meeting of the American Society of Zoologists, 27–30 December 1985, at Baltimore, Maryland.

[2] I would like to dedicate this article to John A. Moore, whose inexhaustible idealism and clear conceptual expositions of wide areas of biology have inspired and set standards for two generations of students, teachers, and authors; his textbook *Principles of Zoology* introduced me to "science as a way of knowing" nearly 30 years ago.

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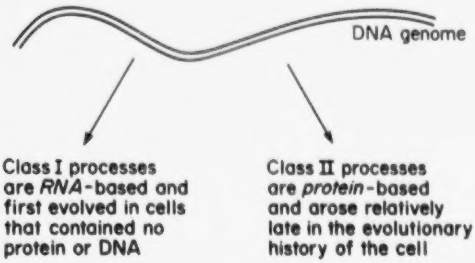
DNA genome
Class I processes are *RNA*-based and first evolved in cells that contained no protein or DNA
Class II processes are *protein*-based and arose relatively late in the evolutionary history of the cell

FIG. 1. As indicated, the DNA genome in today's cells specifies two classes of catalytic mechanisms, here designated as class I and class II. Many of the catalysts in each class evolved before cells contained DNA (see Fig. 8, below).

Today this dogma has become such an integral part of our thinking that many of us find it difficult to imagine any kind of life without DNA. Proteins are also crucial, being the end product of the pathway. They form the enzyme catalysts that determine what reactions occur in cells, as well as ensuring the necessary coordination between these reactions. RNA in this scheme is left with a subsidiary role, acting mainly as a "messenger boy" to carry out the instructions for protein synthesis that emanate from the DNA. This is the picture that emerges in all current textbooks, and it is what all of us teach to our students.

How far have the mighty fallen! For there is every reason to believe that, as far as life is concerned, RNA used to be at center stage. For example, it now seems certain that DNA was only a relatively late addition in the evolutionary history of the cell. Before there was DNA, RNA played the informational role in cells, specifying proteins by itself. And what about earlier, even before proteins? Many of us used to think that there could have been no life before proteins. This view has been shattered in the last few years by the startling (but in retrospect quite reasonable) discovery that RNA molecules can fold in complex ways that give them the same type of highly-specific and sophisticated catalytic activity that biochemists previously associated only with enzymes (Cech, 1985; Cech and Bass, 1986). It is the widespread implications of this revolutionary finding that I wish to discuss here, emphasizing the important contributions this discovery makes to our understanding of cells today.

RNA MOLECULES CAN FUNCTION AS HIGHLY-SELECTIVE CATALYSTS

Efficient enzyme-like catalysis by a protein-free RNA molecule was first discovered in a rather obscure organism—the ciliated protozoon *Tetrahymena*. A *Tetrahymena* ribosomal RNA molecule had been shown to be produced from a larger RNA precursor molecule by RNA splicing, an event that seems to be ubiquitous in eucaryotic cells. (In RNA splicing, two noncontiguous stretches of RNA sequence in an RNA molecule are joined together with the concomitant removal of the nucleotide sequence between them; the latter sequence is called an *intron* sequence and it is normally discarded by the cell.) The surprise came when the scientists attempted to reproduce the ribosomal RNA splicing reaction in an *in vitro* system, so as to be able to study its mechanism. Although it was assumed that the reaction was catalyzed by enzymes, and thus would require a protein extract of lysed *Tetrahymena* cells, the control reactions in which the protein-free RNA was incubated without enzymes also underwent the splicing reaction (Cech *et al.*, 1981; Kruger *et al.*, 1982). It was subsequently shown that the intron sequence itself has an enzyme-like catalytic activity which carries out the reaction in two steps (Fig. 2).

More recently, the 400 nucleotide intron sequence has been synthesized in a test tube and studied in isolation from the rest of the ribosomal RNA transcript (Cech *et al.*, 1983; Bass and Cech, 1984). This sequence folds up to form a complex surface that functions like an enzyme in several reactions. For example, it can bind two specific substrates tightly ($K_m \simeq 10^{-5}\ M$)—a guanine nucleotide and an RNA chain, catalyzing their covalent addition and severing the RNA chain at a unique sequence (Fig. 3).

In this model reaction, which mimics the first step in Figure 2, the same intron sequence can act over and over to cut many different RNA substrate chains. Although autocatalyzed RNA splicing is relatively rare, self-splicing RNAs with intron

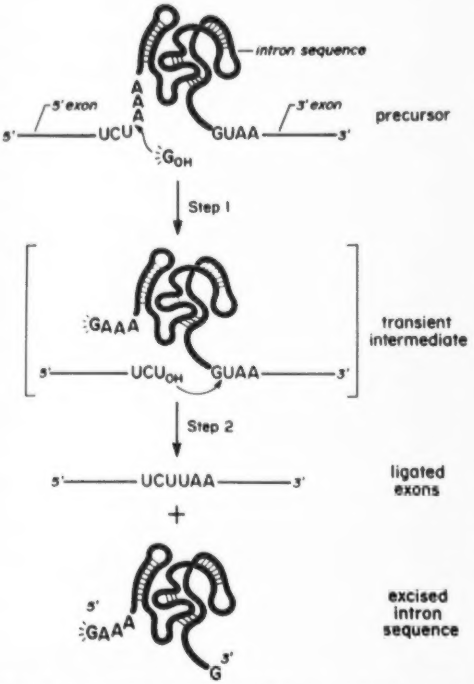

FIG. 2. Diagram of the self-splicing reaction in which an intron sequence catalyzes its own excision from a *Tetrahymena* ribosomal RNA molecule. As shown, the reaction is initiated when a G nucleotide adds to the intron sequence and cleaves the RNA chain; the new end of an RNA chain created then adds to the other side of the intron to complete the process (Zaug *et al.*, 1983).

nucleotide sequences that are related to the one found in *Tetrahymena* have been discovered in other types of cells, including fungi and bacteria (Garriga and Lambowitz, 1984; Belfort *et al.*, 1985). It has therefore been suggested that this RNA sequence may derive from a very ancient one, predating the time that the eucaryotic and procaryotic lineages branched off from each other about 1.5 billion years ago. Other families of catalytic RNAs also exist; for example, an RNA-protein complex that recognizes tRNA precursors and cleaves them at specific sites has RNA and not protein as its major catalyst (Guerrier-Takada *et al.*, 1983). Last but not least, the ribosome itself—lying at the center of cellular biochemistry as the mediator of protein synthesis—is now thought to be an RNA-based catalyst. Most of the ribosomal proteins are suspected to play only a supporting role to the ribosomal RNAs, which make up more than half of the mass of the ribosome and are postulated to have direct catalytic roles in protein synthesis (Woese, 1980; Noller, 1984).

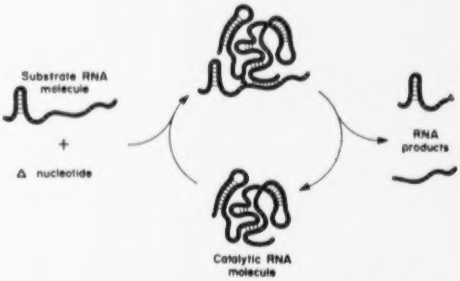

FIG. 3. Schematic diagram of an enzyme-like reaction catalyzed by the purified *Tetrahymena* intron sequence. In this reaction, which models step 1 in Figure 2, both a specific substrate RNA molecule and a G nucleotide become tightly bound to the surface of the catalytic RNA. The nucleotide is then added to the substrate RNA molecule, cleaving it at a specific site. The release of the two RNA product chains frees the intron sequence for further cycles of reaction. This figure is based on unpublished experiments that have been independently carried out by T. Cech and J. Szostack (personal communications).

How is it possible for an RNA molecule to act like an enzyme? It is misleading to think of RNA as a linear polymer containing occasional Watson-Crick base-pair interactions: as do proteins, RNA molecules often fold up in highly specific ways. Most of what we know about RNA folding has been derived from structural studies of a family of unusually short RNA molecules, the transfer RNAs. These molecules, which are only about 70 to 90 nucleotides long, have the three-dimensional conformation outlined in Figure 4B, as determined by X-ray crystallographic analyses (Rich and Kim, 1978). The highly folded molecule is held together by a substantial number of tertiary bonding interactions, some of which are indicated on the simple "cloverleaf" representation of the same tRNA molecule in Figure 4A. Thus, it is incorrect to think of RNA as being capable of only simple Watson-Crick base pairing. Once one admits the possibility of tertiary bonds, it is easy to see how larger

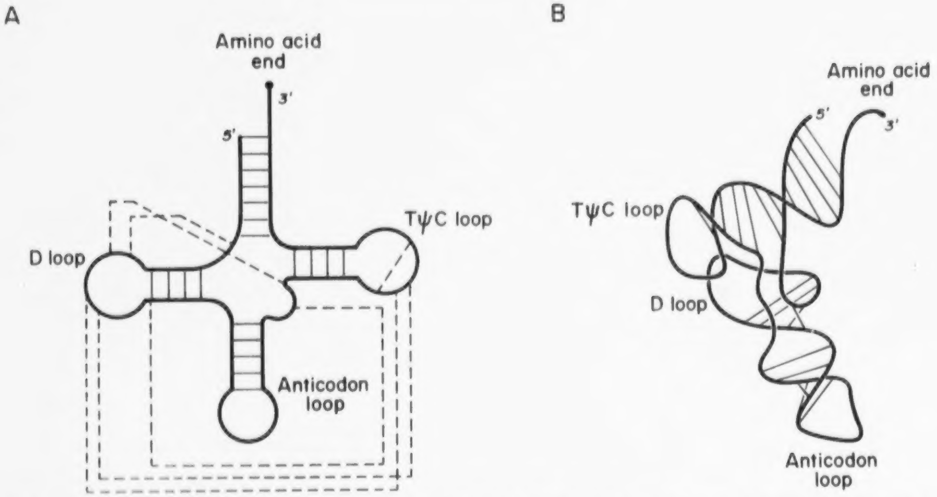

FIG. 4. An outline of the structure of a transfer RNA (tRNA) molecule. (A) A two dimensional view of the structure, shown in its open "cloverleaf form." The thin solid lines represent base pairs in short double-helical regions. The dotted lines connect some of the nucleotides that form tertiary bonding interactions with each other in the folded form that is illustrated in (B) (for further details, see Rich and Kim, 1978).

RNAs, such as the 400 nucleotide intron sequence just discussed, can fold up to form very complex and sophisticated surfaces with a powerful catalytic activity.

IN THE FIRST CELLS, RNA MOLECULES MAY HAVE FUNCTIONED BOTH AS THE SOURCE OF GENETIC INFORMATION AND AS THE MAIN CATALYSTS

The catalytic potential of folded RNA molecules makes it much easier to imagine how the first cells arose on the earth. One suspects that a crucial early event was the evolution of an RNA molecule that could catalyze its own replication, thereby reproducing itself by autocatalysis (Fig. 5, stage 1). Eventually, evolution would select for a mutually-supportive collection of catalytic RNA molecules, some catalyzing the replication of the others (Fig. 5, stage 2). For example, one of these catalytic RNAs might have helped in the production of nucleotide precursors for RNA synthesis. Another might have catalyzed the accumulation of lipid-like molecules to form primitive membranes that isolated each self-replicating RNA family from its neighbors. Once such primitive "cells" were formed, very efficient cycles of mutation and natural selection would occur: different collections of mutually-supportive RNA molecules could now be selected for their increasing fitness as self-reproducing units (Eigen *et al.*, 1981).

Under the pressure of evolution, the RNA molecules in these primitive RNA-based cells would be expected to acquire many of the same properties that enzymes have in cells today. For example, some of these RNAs presumably bound small molecule "coenzymes" to their active surface, which allowed them to increase the chemical versatility of their catalyses. Moreover, to permit homeostasis, feedback regulation could have evolved; such regulation would be mediated through allosteric changes in the structure of RNA catalysts caused by the binding of specific metabolites. Finally, RNA molecules could have harnessed chemical energy to do useful work through organized allosteric changes in their shape; as is found for proteins, the energetically-favorable hydrolysis of ligands bound to the RNA surface could induce these shape changes. Now that we realize that RNA molecules can be such powerful catalysts, it seems reasonable to postulate that RNA-based cells of this type

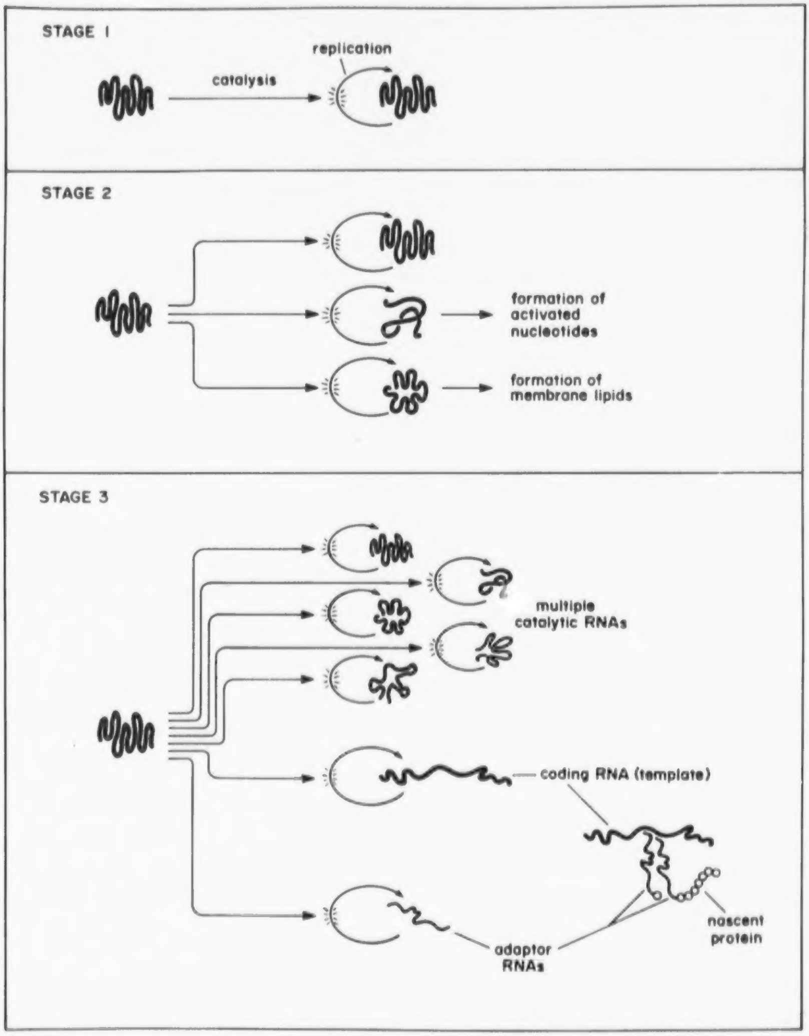

FIG. 5. Schematic illustration of some possible early stages in the evolution of cells. In stage 1, an RNA molecule that catalyzes its own synthesis is illustrated. In reality, such autocatalysis of replication may have required a set of several RNA molecules. The first cells are suggested to have formed in stage 2, when membranes enclosed a set of mutually-supportive catalytic RNA molecules. In stage 3, protein synthesis evolved in these RNA-based cells.

became quite sophisticated chemically. This hypothesis also makes it much easier to understand how the complex process of protein synthesis eventually evolved.

The chemistry involved in protein synthesis presumably developed over a long period of time. Initially, various catalytic RNA molecules would have experimented with joining amino acids together without a template; in this way they could produce short peptides with useful chemical reactivities. In its first version, template-directed protein synthesis probably required only a coding RNA molecule and a set of "adaptor RNAs," as illustrated in Figure 5 (stage 3). The early adaptors, the

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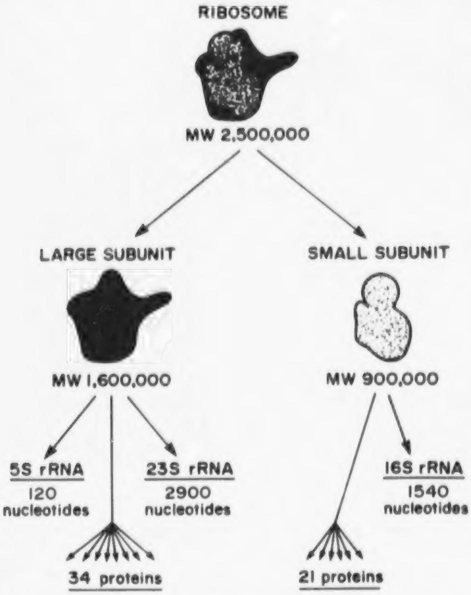

FIG. 6. The structure of the bacterial ribosome. More than 60 percent of the mass of the ribosome is RNA, the remainder being protein (Lake, 1985).

precursors of modern transfer RNAs, are likely to have bound specific amino acids directly, activating them for the subsequent synthesis of polypeptides without requiring other catalysts (Crick, 1968). Obviously, there must have been a relatively simple set of adaptor RNAs and only a limited repertoire of amino acids in such early cells (Crick, 1968; Orgel, 1968; Crick *et al.*, 1976; Hopfield, 1978; Woese, 1980; Crothers, 1982).

Another important early development in protein synthesis was presumably the evolution of new RNA-catalysts that promoted adaptor RNA binding to the coding RNA strand and the subsequent polymerization of the amino acids attached to these adaptors. These catalysts would have been the precursors of modern ribosomal RNA molecules.

While the general evolutionary pathway sketched in Figure 5 seems reasonable, the details are not crucial for the subsequent arguments. The important point is that, whatever the evolutionary pathway, protein synthesis must have evolved in a cell that lacked proteins as we now know them. It is therefore clear that specific RNA molecules were the major catalysts that made the evolution of protein synthesis possible.

NOTHING ABOUT PROTEIN SYNTHESIS MAKES SENSE EXCEPT IN THE LIGHT OF EVOLUTION

Today, protein synthesis is catalyzed by the ribosome, an enormously complex machine whose structure is outlined in Figure 6. The ribosome is composed of a large and a small subunit, which in bacteria contain a total of three ribosomal RNAs and more than 50 different proteins (Lake, 1985). More than 60 percent of its mass is RNA, which was originally thought to play a structural role, helping to position the ribosomal proteins. However, attempts to find specific proteins that catalyze peptide bond formation failed, and it is now widely believed that the ribosomal RNA is itself the major catalyst (Noller, 1984; Moore, 1986). This view is supported by the evolutionary conservation of the RNA components of the ribosome: the structures of the ribosomal RNA molecules appear to be highly conserved, being similar in organisms as diverse as bacteria and humans (Noller, 1984; Gutell *et al.*, 1985).

An outline of the structure of the ribosomal RNA molecule in the small subunit of bacterial ribosomes is presented in Figure 7. This representation is only two-dimensional, being analogous to the view of the tRNA molecule shown earlier in Figure 4A. We do not yet know how this molecule folds up into its compact three-dimensional form, but with a size twenty times larger than a tRNA molecule, the possibilities for creation of a complex and interesting surface are certainly impressive.

I would like to stress two facts about the ribosome. First, its catalysis of protein synthesis appears to be an RNA-based process, as expected from the pathway by which the process of protein synthesis evolved (Fig. 5). Second, the mechanism of protein synthesis seems complex and awkward compared to other biological processes that evolved later and were therefore based on protein catalysts (this point will be explored later, when we discuss DNA replication as a class II reaction). Some important, although tentative, conclusions can be derived from these two observations. It seems, first of all, that RNA-based catalyses are considerably less powerful than protein-based catalyses. As a consequence, it takes much more molecular mass to carry out a reaction catalyzed by RNA molecules than to carry out the same reaction catalyzed by proteins. In terms of a familiar analogy, the early cells that used only RNA catalysis were like a computer based on vacuum tube technology: very slow for their size. This is presumably why those cells that developed protein synthesis proliferated at the expense of their neighbors, and came to dominate the earth to such an extent that no cells lacking proteins have survived.

If they are less efficient than protein catalysts, why do any RNA catalysts still exist in cells? The suggestion is that cells, unlike those of us who have recently purchased computers, have been unable to escape the past. Thus, while a "microchip solution" to the synthesis of proteins would presumably be more efficient for the cell, the old mechanism clearly works well enough in its present patched-together form (in which ribosomal proteins have been added on as appendages to help the ribosomal RNAs) to be retained. In other words, cells—unlike computers—are not optimally designed. Instead what they are today is in large part a reflection of their past history (Jacob, 1977). The ribosome is a notable example. As a machine for making proteins, the ribosome seems so awkward as to be a bore both for teachers to teach and for students to learn. Its many pieces seem to make no conceptual sense at all, especially when compared to the elegantly-designed pieces of a DNA replication machine (see below). Only when viewed as a historical relic does the ribosome come alive. Now it suddenly turns into a fascinating object that can help us to understand the pathway by which protein synthesis evolved, and even how early cells might have worked before there were proteins.

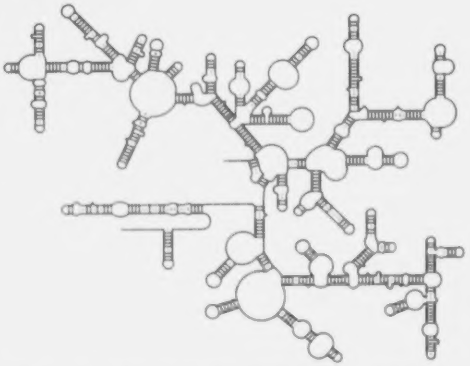

FIG. 7. The structure of 16S rRNA, the RNA molecule in the small subunit of bacterial ribosomes. Only a two-dimensional view of this molecule, which contains 1,542 nucleotides, is shown; how the molecule is folded in three dimensions in unknown (courtesy of H. F. Noller; from Gutell *et al.*, 1985).

ALL DNA FUNCTIONS EVOLVED IN AN ENVIRONMENT RICH IN PROTEIN CATALYSTS

If history still shows in a cell as claimed, then knowing the path by which the cell evolved should be useful for understanding many cellular processes. In present-day cells, a great deal of action centers on DNA and the manner in which gene expression is controlled. Yet DNA itself is generally considered to have arisen only at a relatively late step in the evolution of the cell. As outlined in Figure 8, the postulated RNA-based cells were succeeded by cells in which proteins carried out more and more of cellular catalysis. As these cells became more complex and sophisticated, there would have been pressure to evolve specialized RNA molecules that stored the cell's genetic information in an RNA double helix (Strickberger, 1986). In this form, each nucleotide sequence would be stored in duplicate, and RNA repair mechanisms (analogous to present-day DNA repair mechanisms) could operate to stabilize the genetic information against the inevitable random damage that is inflicted by chemical decay. Only in this way could the many

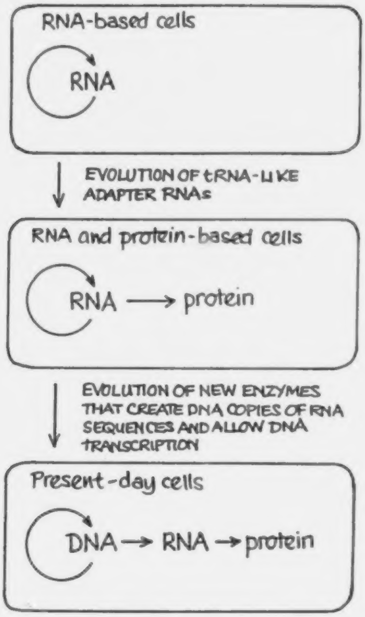
RNA-based cells
RNA
EVOLUTION OF tRNA-LIKE ADAPTER RNAs
RNA and protein-based cells
RNA ⟶ protein
EVOLUTION OF NEW ENZYMES THAT CREATE DNA COPIES OF RNA SEQUENCES AND ALLOW DNA TRANSCRIPTION
Present-day cells
DNA → RNA → protein

FIG. 8. Three postulated steps in the evolution of cells, culminating in the central dogma. Because DNA is a relatively late addition to the cell, it is likely that many enzymes evolved to an advanced state in cells that lacked DNA.

sequences of nucleotides required to specify complex cells be stably maintained.

RNA differs from DNA in having an extra 2′OH group on each of its sugars. The extra hydroxyl groups on RNA molecules are no doubt very important for imparting specific catalytic activities to its various folded forms. This difference is sufficient to explain why RNA and not DNA was the nucleic acid that formed the basis for the first cells. But the same chemical reactivity that is useful for catalysis is harmful in a molecule designed to store genetic information because it increases the rate of spontaneous chemical decay processes. It is presumably for this reason that double-stranded DNA evolved to take the place of RNA as the nucleic acid that stores the genetic information in present-day cells. The replacement process must have occurred gradually, with the evolution of intermediate cells containing both RNA and DNA information stores. During this period, a large entourage of new enzymes had to be developed to handle DNA—including RNA polymerase and a variety of gene regulatory proteins.

The pressure to switch to a more stable genome should have arisen after cells became reasonably complex, and carried so much nucleotide sequence information that the increased chemical stability of DNA was important. It therefore seems safe to assume that DNA became the main information store in cells only relatively late in cell evolution. Because such cells would have contained a large number of very efficient protein catalysts, the various DNA functions must have evolved in an intracellular environment where RNA catalysis had become largely obsolete. Accordingly, by our arguments one would expect all of the processes occurring on DNA to be carried out by mechanisms that are much more efficient than those found for protein synthesis, with protein catalysis being used exclusively (*i.e.*, no RNA catalysis).

DNA REPLICATION DEMONSTRATES THE POWER OF PROTEIN CATALYSIS

DNA replication is an example of a process that occurs on DNA by a mechanism that is well understood (Kornberg, 1980). For this reason, it serves as a good model of a late-evolving catalytic mechanism and provides a useful comparison to protein synthesis. The action takes place at a structure called a "replication fork"; here the parental DNA double helix is opened into its two separate strands, so that each old strand can serve as a template for the formation of a new strand. As a result, two daughter DNA double helices are formed, each with one old strand and one new strand (the so-called semiconservative mode of DNA synthesis that was predicted by Watson and Crick [1953]).

A number of proteins with discrete functions are involved in moving a replication fork, and these cooperate to form a multienzyme "protein machine" that synthesizes DNA (Alberts, 1985). The replication fork with its bound proteins is displayed in a two-dimensional representation in Figure 9. Because the two strands of the DNA double helix are oriented in opposite direc-

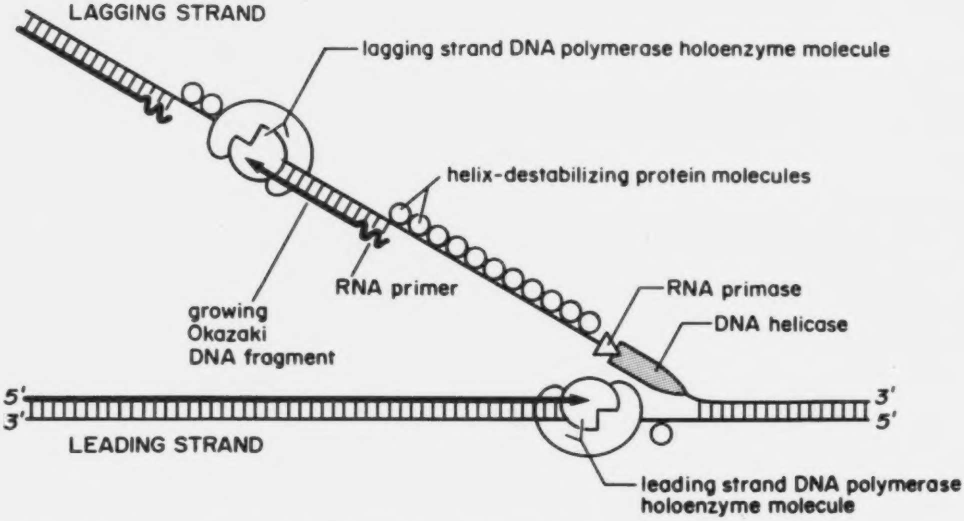
LAGGING STRAND
lagging strand DNA polymerase holoenzyme molecule
helix-destabilizing protein molecules
RNA primer
growing Okazaki DNA fragment
RNA primase
DNA helicase
5'
3'
3'
5'
LEADING STRAND
leading strand DNA polymerase holoenzyme molecule

FIG. 9. A two-dimensional view of the DNA replication fork, showing the major proteins present (see text for details).

tions, while the polymerization of nucleotides occurs only in one direction, the replication fork is asymmetric—with "leading" and "lagging" strands. The actual synthesis of DNA is catalyzed by a complex of several proteins called a DNA polymerase "holoenzyme," with a separate polymerase molecule on each strand. The DNA polymerase on the leading strand moves continuously, whereas the other DNA polymerase molecule works discontinuously, being forced by the orientation of its template strand to synthesize the lagging strand as a series of short Okazaki fragments. Behind the replication fork, these fragments are stitched together by a DNA repair process, creating a continuous daughter DNA strand.

The cell was faced with several technical problems in the design of the replication mechanism, and these were solved by the evolution of a variety of cooperating replication proteins. First of all, the DNA helix ahead of the replication fork had to be opened at a rapid rate, exposing the DNA bases on the template in a single-stranded form. This problem is solved by a DNA helicase molecule that uses ATP hydrolysis energy to propel itself rapidly along a DNA single strand (Fig. 10). This enzyme runs along the lagging strand at the fork, pushing open the helix ahead of it as it goes. Helix-destabilizing protein molecules help the helicase by binding in clusters to the newly-opened DNA strands; these protein molecules manage to bind tightly to a DNA single strand while leaving the DNA bases on the strand freely available for base pairing (see Fig. 9, above).

A second problem is that all DNA polymerases require a 3'OH end on which to polymerize nucleotides; this pre-existing "primer chain" must be base-paired to the template strand to be copied (Kornberg, 1980). Thus, the synthesis of every Okazaki fragment must be started by a separate oligonucleotide primer. The primer used for this purpose is a short RNA molecule, which is synthesized by a separate enzyme called an *RNA primase*; this primase enzyme is kept at the proper position on the lagging strand by virtue of its attachment to the moving DNA helicase (see Fig. 9, above).

The replication fork in three-dimensions is even more impressive. As shown in Figure 11, the DNA on the lagging strand of the fork is apparently folded back on

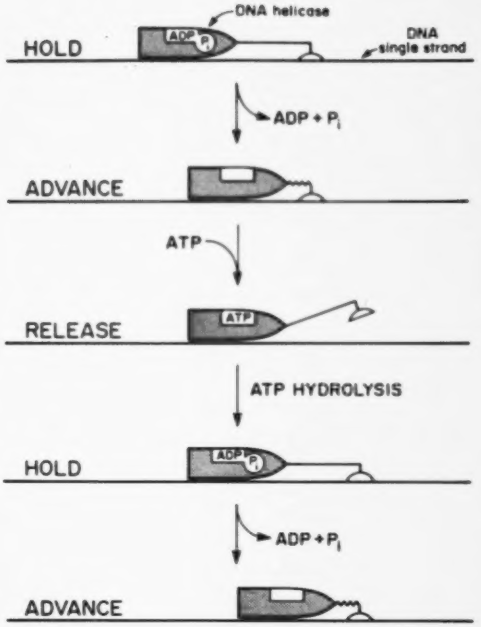

FIG. 10. Schematic diagram showing how a DNA helicase is moved along a DNA strand by allosteric changes in its conformation caused by the hydrolysis and release of ATP molecules. The fact that one of the conformational transitions is directly coupled to ATP hydolysis makes this cycle of three shape changes unidirectional. As a result, the helicase moves consistently in a single direction along the DNA, as shown. The rate of helicase movement in bacterial cells is about 500 nucleotides per second.

itself to allow the lagging strand DNA polymerase molecule to form a complex with the leading strand DNA polymerase molecule. This linkage makes it possible for the DNA polymerase molecule on the lagging strand to be used over and over for successive rounds of Okazaki fragment synthesis, as schematically illustrated in Figure 12.

The entire set of replication proteins acts like a tiny sewing machine, powered by nucleoside triphosphate hydrolyses that move the individual protein parts relative to each other without disassembly of the complex. The mechanism is incredibly efficient: in bacteria, the replication fork moves at a rate of about 500 nucleotides per second, and the fidelity of templating is such that less than one nucleotide incoporation error is made per every 10^8 base pairs replicated. Compare this performance with that of a ribosome, where proteins are synthesized at a rate of only 20 amino acids per second with about one error in every 10^4 amino acids polymerized. Yet the ribosome has a total mass more than three times greater than that of the replication apparatus. In my opinion, this state of affairs does not make sense unless we view the ribosome as a historical relic that evolved during an age where cells were capable only of "vacuum tube technology."

THE MECHANISMS USED FOR NUCLEAR PRE-mRNA SPLICING SUGGEST THAT THIS REACTION IS OF ANCIENT ORIGIN

Eucaryotic cells evolved from procaryotic cells, and yet only eucaryotes make extensive use of an externally-catalyzed form of RNA splicing that removes internal sequences (intron sequences) from their primary RNA transcripts (Chambon, 1981). Therefore, either bacteria have lost an old mechanism (Gilbert, 1978), or nuclear pre-mRNA splicing evolved relatively late in cell evolution. Recent biochemical studies probing the mechanism of the eucaryotic type of RNA splicing have revealed that the reaction is carried out by a large complex of ribonucleoprotein particles, whose total size approaches the size of a ribosome (Brody and Abelson, 1985; Grabowski *et al.*, 1985). According to our arguments, this reaction should therefore be an ancient one that first evolved in RNA-based cells and was present in the ancestors of all bacteria.

EUCARYOTIC GENE EXPRESSION, LIKE DNA REPLICATION, IS LIKELY TO BE MEDIATED BY PROTEIN MACHINES

The control of eucaryotic gene expression is currently an area of intense research. These controls program the cells in a multicellular organism to become different according to their position during embryonic development, as required to produce a complex organism. Whether a particular gene is expressed or not can probably be regulated at any one of the many different steps required to translate a DNA sequence into a protein sequence. However, the pre-

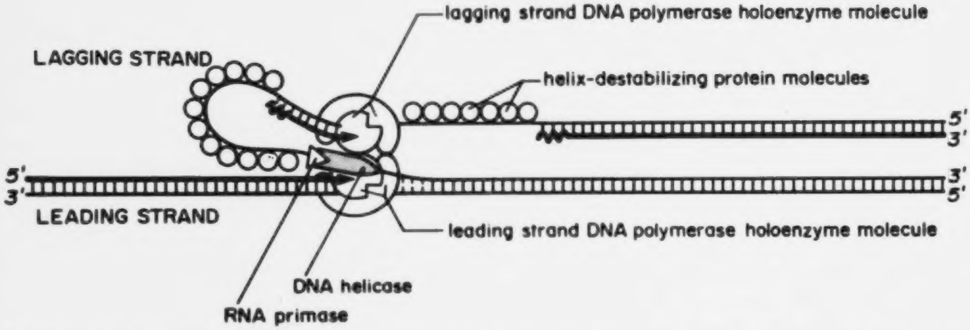
lagging strand DNA polymerase holoenzyme molecule
LAGGING STRAND
helix-destabilizing protein molecules
5'
3'
5'
3'
3'
5'
LEADING STRAND
leading strand DNA polymerase holoenzyme molecule
DNA helicase
RNA primase

FIG. 11. The proteins of a DNA replication machine as they are thought to exist in an actual replication fork. The two-dimensional replication fork in Figure 9 has been converted into the structure shown by folding the DNA on the lagging strand in such a way as to bring the DNA polymerase on the lagging strand close to the DNA polymerase molecule on the leading strand. The lagging strand DNA polymerase molecule is thereby held to the rest of the replication proteins, allowing it to be retained for many successive cycles of Okazaki fragment synthesis, as shown in Figure 12.

dominant level of control is exerted at the first step of gene expression, when the decision is made to transcribe a given region of the DNA into RNA (Darnell, 1985). This level of control also predominates in bacteria, where many of the mechanisms involved have been worked out in great detail (Lewin, 1985). Here proteins bind to specific DNA sequences about 10 to 20 nucleotides long to control the expression of genes. Such proteins are called *gene regulatory proteins,* and they can either activate or repress the process of transcribing the adjacent region of DNA into an RNA sequence. Repression is an especially simple process. RNA polymerase, the enzyme that synthesizes RNA from a DNA template, binds to a specific DNA sequence called a *promoter* to initiate the process of DNA transcription. Gene regulatory proteins that work as repressors bind to a DNA sequence that overlaps the promoter sequence, preventing RNA polymerase from binding at that site and thereby blocking the transcription of the adjacent gene. Gene activation is only slightly more complicated. In this case, a gene is normally turned off because its promoter sequence is an altered one that RNA polymerase by itself is unable to use efficiently. However, this defective promoter becomes a good promoter for the RNA polymerase when a gene regulatory protein binds to a specific DNA sequence just upstream. During such gene activation, the gene regulatory protein is believed to touch the RNA polymerase at the adjacent promoter site in a way that helps this enzyme to begin its RNA synthesis (Ptashne *et al.*, 1980).

In bacteria, both gene activation and gene repression usually involve the binding of gene regulatory proteins at or very near to the promoter, which in turn contains the start site for RNA synthesis. There are some theoretical reasons why one might expect a difference between bacterial and eucaryotic gene control mechanisms in this regard. A gene in a complex multicellular organism appears to turn on or off in response to the sum of many different inputs, and we now know that the controlling mechanism interprets the cumulative effect of many gene regulatory proteins acting simultaneously on each gene (Yamamoto, 1985). This type of *combinatorial* control is advantageous for the cell, because it allows a large number of genes to be regulated by relatively few gene regulatory proteins (Gierer, 1974). It is not clear how such multifactorial combinatorial control would be accomplished by the simple type of mechanism just described, where only a small region on the DNA is alloted for regulating a gene's activity.

Fortunately for theorists, when investigators started dissecting the mechanisms of eucaryotic gene regulation through the use of recombinant DNA methods, a some-

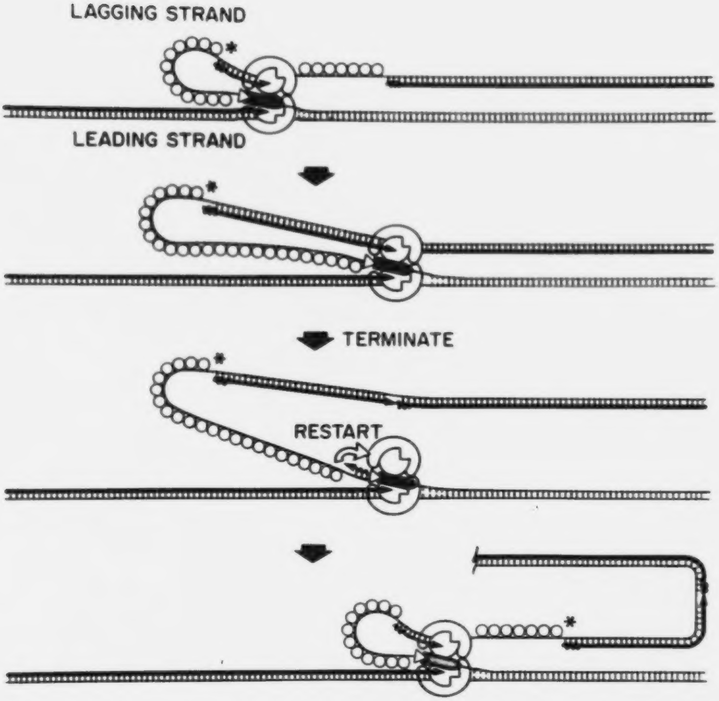

FIG. 12. A model for the movement of the replication fork shown in Figure 11. The crucial step in the cycle shown occurs when the lagging strand DNA polymerase molecule finishes the synthesis of each Okazaki fragment; in this "termination" step, the DNA on the lagging strand is released, freeing the polymerase to start the next Okazaki fragment. As indicated, the termination event also appears to trigger the synthesis of an RNA primer by the adjacent molecule of RNA primase (from Alberts, 1985).

what different form of gene regulation was discovered. Although gene regulatory proteins that bind to specific DNA sequences are again involved, one class of these can control the transcription of eucaryotic genes by binding to a site that is hundreds to thousands of DNA base pairs away from the promoter sequence at which RNA polymerase starts. Moreover, the sites that bind these proteins can be experimentally relocated at many different positions relative to the promoter without losing their effect. While most such sites are located upstream from the transcription start site, sometimes they are found in the middle of a transcribed DNA sequence or even at the far end of a gene. The first such gene control sites found were called "enhancers" (Serfling *et al.*, 1985), because when they bound a gene regulatory protein the transcription of a nearby gene increased (Fig. 13A). More recently, sites that seem to act in the opposite way—turning off genes from a distance—have been discovered (Brand *et al.*, 1985; Johnson and Herskowitz, 1985; Struhl, 1985); these sites have tentatively been called "silencers" (Fig. 13A).

As more and more information has been obtained concerning the regulatory regions near higher eucaryotic genes, it has become apparent that many eucaryotic genes have the general structure that is schematically illustrated in Figure 13B. Whether a gene is on or off depends on the sum of multiple inputs from a number of different gene regulatory proteins, some tending to turn the gene on and others tending to turn the gene off. These regulatory proteins bind to specific sites that can be scattered over

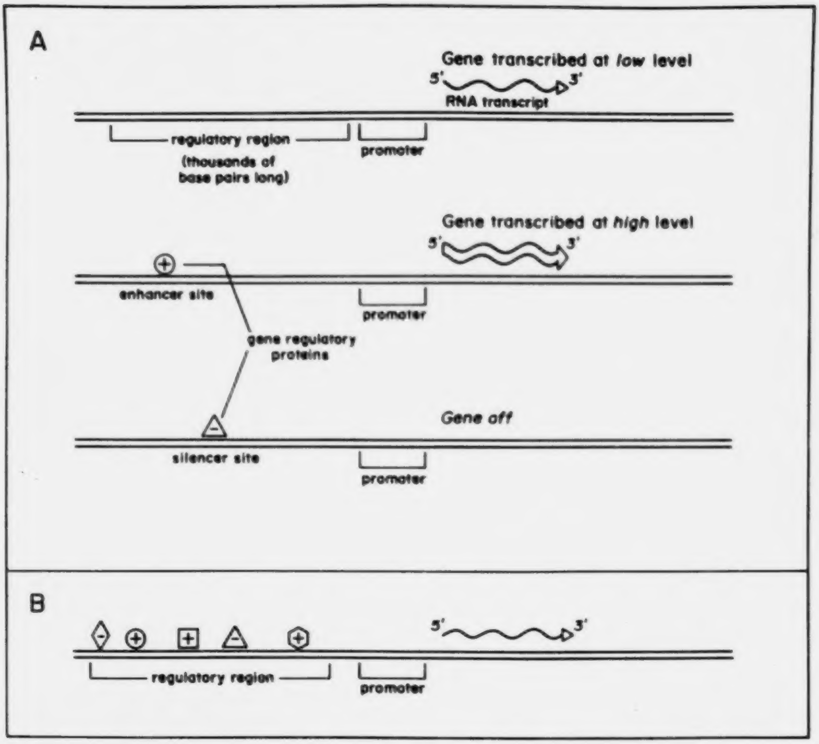

FIG. 13. Diagram illustrating the control of eucaryotic gene expression by gene regulatory proteins that bind to enhancer and silencer sites. The same gene is shown in three different states of activity in (A). In (B), a eucaryotic gene is shown that is regulated by the combined action of many different gene regulatory proteins. Such combinatorial gene regulation is common in eucaryotes.

a region of the DNA that is 5,000 or more base pairs long. By unknown means, the signals from all of these protein binding sites are integrated to control DNA transcription at the promoter.

Our knowledge of the effect of different enhancer and silencer sites on the patterns of gene expression in an organism is increasing especially rapidly in *Drosophila*, where mutants in a series of different gene regulatory proteins have been identified by geneticists, each of which has a major effect on patterns of gene expression in the early embryo (Lewis, 1978; Nusslein-Volhard and Wieschaus, 1980; Mahowald and Hardy, 1985). Several such regulatory genes have now been characterized and shown to be expressed in highly-specific spatial patterns across the early 6,000-cell blastoderm embryo (for example, see Hafen *et al.*, 1984; Kornberg *et al.*, 1985). These spatial patterns of gene expression change when other putative gene regulatory proteins are mutated in the embryo, and it is thought that many of the gene regulatory proteins defined by these mutants affect each others' syntheses (Desplan *et al.*, 1985; Struhl and White, 1985). Specific alterations in patterns of gene expression are also observed when different short sections of DNA, each apparently containing one or more enhancer or silencer sites, are removed from the regulatory region next to a gene (Hiromi *et al.*, 1985).

As yet, biochemical studies of the mechanism by which enhancers and silencers act to control eucaryotic gene expression have lagged far behind the physiological studies that have defined these elements. Thus, how the gene regulatory proteins act from a distance and how effects from different sites are combined and interpreted remain unknown. Another important unknown is how "cell memory" works—*i.e.*, how cells in eucaryotes can inherit a gene that remains either on or off in a cell clone (Brown, 1984).

In the context of this article, it is worth remembering that all these mechanisms of eucaryotic gene expression must have evolved quite late in the evolutionary history of the cell. Thus, while the mechanisms are not known, we can expect them to resemble DNA replication in being catalyzed by elegant and efficient protein machines. This means, first of all, that one expects proteins and not ribonucleoprotein particles to be involved. Second, one should not be surprised to find systems of interacting proteins that move relative to each other without dissociating, some of which hydrolyze nucleoside triphosphates to create ordered conformational changes in either the DNA or themselves. It should be a fascinating story, with many of the details appearing in the next ten years. Be sure to keep tuned!

CONCLUSIONS AND CAVEATS

In this report I have suggested that cells contain two broad classes of catalytic mechanisms. Class I mechanisms are processes that are carried out by large ribonucleoprotein complexes and appear to involve RNA catalysis. Two examples are protein synthesis and RNA splicing. These mechanisms seem complicated and unwieldy, and are best explained as historical relics of processes that arose early in the evolution of the cell, when only relatively inefficient catalysts were available. Class II processes do not involve RNA catalysis; instead they are likely to be carried out by multienzyme "protein machines." An example of such a mechanism is DNA replication. These mechanisms seem elegant and efficient when compared to class I mechanisms. They are likely to have evolved later, during a period when cells contained a large repertoire of very efficient protein catalysts. This binary characterization of catalytic reactions is no doubt oversimplified, but it seems useful in two respects. First of all, as witnessed by our discussion of nuclear pre-mRNA splicing, this view can allow the origin of a biological process to be positioned with respect to the evolutionary history of the cell, once its mechanism is known. Second, it predicts that the mechanisms used for all DNA-mediated processes will resemble those found for DNA replication much more than those found for protein synthesis. Such a prediction is of practical value, since most of these mechanisms are not yet well-understood, and the optimal experimental approach to deciphering them can depend on the type of catalysis involved (for example, see Alberts, 1984).

The above analysis incorporates several unproven assumptions, some of which may not be obvious to most readers. First of all, previous discussions of the origin of protein synthesis have usually assumed that this process originated in a relatively primitive, pre-cellular "soup" of macromolecules, and therefore that there were no cells before there were proteins (*e.g.*, see Eigen *et al.*, 1981). In my opinion, the recent discovery of efficient catalysis by RNA molecules makes it unreasonable to insist that cells could not exist without proteins. In turn, the possibility of RNA-based cells allows protein synthesis to evolve in the presence of a sophisticated family of RNA catalysts, making the spontaneous origin of genetically-specified proteins on the earth seem much more feasible from a chemical standpoint.

There is a second important assumption that needs to be exposed. The two processes that I have termed class I reactions—protein synthesis and nuclear pre-mRNA splicing—both involve the accurate recognition of nucleotide sequences in single-stranded RNA molecules. One could therefore explain the observed role of ribonucleoprotein complexes in these reactions simply by postulating that proteins by themselves have a great deal of difficulty in recognizing specific sequences in a folded nucleic acid chain, and that such recognitions are best accomplished by a second polynucleotide sequence (Cech and Bass, 1986). In such a view, RNA catalysts are present in cells not because they are historical relics, but because they can accomplish certain types of catalyses better than protein molecules alone. It is hard for me to accept this hypothesis, because specific nucleotide sequences in single-stranded DNA chains are known to be recognized very rapidly and efficiently by proteins during DNA replication (*e.g.*, see Eisenberg *et al.*, 1977; Schlomai and Kornberg, 1980; Tabor and Richardson, 1981; Cha and Alberts, 1986). However, we can never be certain that it is possible to design an RNA-free protein machine that would improve upon protein synthesis—unless of course someone discovers a novel bacterium that can divide every two minutes by making proteins without ribosomes!

In this article, I have consistently stressed the relative inefficiency of RNA catalysts in comparison to protein catalysts. However, it is important to realize that the RNA molecules in the first cells must have been considerably more diverse and sophisticated as catalysts than the very limited set of catalytic RNA molecules thus far known. While most of these early catalysts would have undergone extinction when more efficient protein catalysts evolved to supplant them, one would expect others to have survived. Detailed studies of various catalyses carried out by ribonucleoprotein particles are now underway; hopefully, some of the results will reveal much more about the fascinating RNA catalysts that are suspected to have made life possible before proteins.

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Patterns of Inheritance[1]

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SYNOPSIS. Every individual living organism on earth develops according to the specifications of its individualized and unique DNA that is encoded as its genotype. The genotype consists of many genes and is established at the time of the individual's birth or separation from its parent. Although offspring resemble parents, they are rarely if ever genetically identical to them. This result is a function of both the pattern of inheritance and the organization imposed by the genetic system embodied in the chromosomes. Genes are not just loose in the nucleus: they are organized into linear arrays on chromosomes. In the diploid, cross-fertilizing genetic system, the parents contribute about equally to the offspring's genotype through the haploid nuclei of their gametes. In most diploids, vast amounts of genetic variability are produced by the process of genetic recombination. This alone assures the genetic uniqueness of every individual of the new generation. The ultimate source of the variability is the process of gene mutation but the great storage capacity of the diploid system enhances recombinational variability. The powerful sources of recombination are: synapsis and crossing-over, processes that serve to scramble the genes. Independent assortment at meiosis provides unique gametes; this latter effect is enhanced by high chromosome numbers. Since two parents are involved in the formation of the individual, still another level of recombination is achieved at fertilization. Patterns of genetic systems vary greatly from species to species: man, mouse, maize and *melanogaster* are considered. In a significant number of cases, chromosome number reductions, balanced chromosomal aberrations and polyploidy are present and serve to restrict recombination potential. Even greater restrictions are imposed by the evolution, in natural populations, of patterns of inheritance that partially or even completely by-pass recombination. Thus, total dependence on vegetative reproduction, loss of meiosis, self-fertilization or parthenogenesis are examples. In organisms that have discarded the attributes that assure recombination, the formation of both new species and new adaptations is impaired. This emphasizes the key importance of the mode of inheritance for activating processes that adjust the genes of living things to their environments. Future studies of patterns of inheritance in relation to the evolution of life on earth are needed.

FOREWORD

This article emphasizes two particular aspects of the living condition: the genetical state of the individual organism and sexual matters relating to the reproduction of the individual. When a biologist deals with such subjects, a problem of communication arises. Every person who happens to read such material considers himself or herself to be an expert, from personal experience, in these areas. Indeed, preoccupation with both self and sex are all-pervading in the lives of most people. Intense familiarity with our own individuality makes it difficult for us to grasp some very important biological aspects of the larger picture. I refer here to the fact that although life and its various species continue unbroken through parent and offspring, it is hard, indeed devastating, for us to grasp the truth of our extreme impermanence as individuals. You and I can live only the proverbial fourscore and ten years and often it is a lot less. Yet around us grows up a younger generation carrying our genes in new and different combinations. In broad perspective, the individual is but a momentary blip on the screen of life, whereas populations and species have a real and enviable longevity.

Why are individuals so impermanent? Modern genetics provides a quite simple explanation. The DNA, that encodes the collective experience of populations past, is momentarily encapsulated in a series of sets of gene combinations that are represented by the single individuals. That, indeed, is the *only* place that one finds DNA in nature, except in the biochemist's freezer. The encoded genes tend to be slowly destroyed or damaged on a day-to-day basis during the individual's life. These alterations of the DNA are the result of gene mutation that begins to erode the genotype even on the first day of its existence in a fertilized egg. Natural selection insists that the individual's genetic combination must be purged and reorganized. The only thing that can save the DNA in the long run is putting it through the mill of reproduction with all of the complexities dictated by the accompanying recombination and selection. These processes are responsible for forging renewed genotypes in the offspring. The individual has been endowed by natural selection with powerful built-in sexual drives that assure at least attempts at reproduction. If the individual dies without reproduction, this is the end of a long unbroken biological past: on the other hand, those that do reproduce, inherit the earth, at least temporarily. Indeed, feelings of sex and self tend to dominate our lives; in this regard we resemble most of the rest of the individuals in the biological world.

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INTRODUCTION

What is a "genetic system"?

Each species of animal or plant reproduces its kind through cells that carry a genetic makeup characteristic of that species. In most cases, the genes are carried on chromosomal structures located within the nucleus of each cell of the individual, including both germ cells and somatic cells. The genetic system of the species, a concept introduced by Darlington (1932) consists of the number, size and genic content of the chromosomes together with the life-history details of the cycles of recombination through which these chromosomes go during meiosis and syngamy.

Accordingly, the genetic system embodies a set of cytogenetic facts that describe chromosome structure and behavior. "Behavior" may seem to some persons a rather peculiar word to use, since in the strict biological sense, only the higher animals have behavior. Yet it is true that the cycles of changes in position and replication that the chromosomes go through during the life cycle are best looked upon as programmed behavioral processes. These behavioral events, expecially as they pertain to cells of the germ line, are of great importance for the understanding of the nature and extent of the genetic variability expressed in the individual members of the species under examination. Thus, the genetic system of a species tends to impose a particular pattern of inheritance on that species. Patterns of inheritance differ not only among some major groups of organisms but there are also usually significant differences even between closely related species.

The purpose of this article is to explore the present extent of knowledge of the nature of and variation in genetic systems. This will serve as a basis for understanding the amount of realized genetic variability within a species. Genetic variability is designated as "realized" when its existence is directly reflected in the phenotypes of individuals.

As the essence of organic evolution involves descent with genetic change, knowledge of the details of the genetic system enables us not only to make some estimate of the past evolutionary history of the species but also may serve as a basis for predicting its evolutionary future.

ORIGIN AND DISTRIBUTION OF GENETIC VARIABILITY

Variation at the level of the individual

The genetic information carried by each individual living organism is encoded in the genes of the chromosomes which that individual received from its parents. The individual receives these chromosomes and combines them into the single-celled zygote. Subsequent growth and development of the individual into an adult organism is accompanied by the distribution of an exact copy of this chromosome set into each cell that is directly descended from the zygote.

This feat, of course, is accomplished by the way in which the chromosomes behave during the process of mitosis. The chromosomes are normally precisely duplicated at each cell division. Basically, this is the most stable process of the entire genetic system. At very infrequent intervals, however, a spontaneous alteration in a chromosome or gene may occur in a single cell. Such mutations are newly-added, that is, they were not inherited from either parent as were the rest of the genes. Like the rest, however, they are permanent and irrevocable. Unless the change is drastic or lethal, all cells descended from the one that acquired the new mutation show the change. Should that change ultimately reach the nucleus of an egg or sperm, the potential exists for it to be passed along to the next generation.

Most mutations reflect a precise biochemical change in the hereditary material itself, the DNA that is carried on the chromosomes. The organization of the DNA, the genes and their subdivisions on the chromosomes is basically linear: the chromosomes are thus elongated structures that have the genes strung out in a line. A gene change may occur at one point in the molecule only; the rest of the string of genes will be unchanged.

Some mutations, however, involve a larger section or indeed a whole chromosome rather than one point of the DNA. These are generally referred to as chromosome mutations. The most important types are inversions, in which a linear section is reversed in order, and translocations, whereby a substantial section of chromosome may be moved to a new site by breakage and refusion. These mutations are often quite drastic in their effect and many types of chromosomal mutants are cell lethals, causing the death of the cell.

What are the ultimate causes of mutant change? Geneticists have for a long time considered the mutation process to be "spontaneous." This designation is to a large degree a cloak for ignorance of the specific cause of the change in a gene or chromosome. Nevertheless, there is now a large amount of information indicating that various agents increase the rate of change. Most prominent among these are such mutagenic agents as ionizing radiation and radiomimetic chemicals. Most of these agents do not act to produce specific mutants but rather generate new variability that is essentially random with regard to the needs of the organism.

In the early days of genetics, much emphasis was placed on the study of single genes that have large phenotypic effects (oligogenes). This attribute makes it possible to use the gene as a marker in studies of meiotic crossing-over and the mapping of genes on chromosomes. From the developmental point of view, these oligogenes have further usefulness in that their effects can sometimes be traced to a particular enzyme in a biochemical pathway in development or in the performance of some essential function.

The existence of genes that have individually minor effects (polygenes) was discovered at an early time in the history of genetics but the difficulties in recognizing such genes individually continue to the present day. Suffice it to say here that, although difficult to deal with individually, genes of minor effect appear to be of great importance from the long-term evolutionary point of view. Their presence tends to modify, or indeed sometimes to regulate, the dictates of large-effect genes. But even beyond that, groups of them, through the recombination processes of the genetic system, come to underlie exceedingly important biological functions and properties of the organism. These are usually referred to as "quantitative traits." They include such attributes of the individual as size, proportionate growth, disease resistance, and various aspects of general vigor and reproductive success. This is not to say that large-effect genes are not involved in the genetic determination of these characters. Rather, it should be stressed that almost every trait that is essential to the daily life of the organism is affected by many individual genes that have been brought into concert by the shuffling process of gene recombination and the sensitive process of natural selection that favors the reproduction of those gene combinations that work best.

Detailed modern molecular analyses of gene structure and function have claimed much attention in genetics in recent years.

Yet, it seems clear that if we are to understand the type of genetic changes imposed by the evolutionary process on the genetic material, it will be necessary to unravel further the details of the inheritance of quantitative characters.

As has been pointed out earlier, the many genes of an animal or plant are not just rattling around loose within the nucleus: they are organized in a linear order on a finite number of chromosomes. The chromosomes of a species have a high degree of individuality; for example, some may be short and others long. In general, the shorter ones have fewer genes than the longer ones; the exceptions to this rule appear to relate to the existence of whole chromosomes, chromosome arms, or sections of an arm, that are made up of repetitive DNAs of certain molecular types. This material, called heterochromatin by the cytologist, appears not to contain important coding information. Its origin and function is still an unsolved puzzle.

We are concerned in this part of the discussion with diploid individuals. By definition, diploids have each member of the chromosome set represented twice, that is, the chromosomes exist in homologous pairs. Ultimately, of course, one member of this pair was contributed to the individual by the male parent and the other by the female parent. Accordingly, the gene content of the two members of the pair are different from one another in that they usually carry different alleles at many loci over their length.

The two members of a chromosome pair are usually quite independent of one another during the mitoses that follow zygote formation and that occur in the somatic tissues throughout the life of the individual. When the chromosomes reach the cells of the reproductive organs and meiosis ensues, the homologues seek out one another in the nucleus and undergo synapsis. This event is followed by the remarkable process of crossing-over, which accomplishes a series of reciprocal exchanges between the two chromosomes.

The next result is that at meiosis in an individual, two homologous chromosomes that are already quite different from one another are capable of producing new recombinant chromosomal strands. The very great initial chromosomal variability in gene content, which is now well documented at the molecular level, results in the production in an individual of a mathematically exuberant amount of new variability in the form of recombined chromosome strands. Each individual of a bisexual species, therefore, is an engine for the generation of this variability.

Crossing-over between homologues is not the end of this process, however, since the recombinant strands are subsequently sorted out into separate cells through the operation of the two meiotic divisions. The essential feature of this latter event is the process of random assortment of the recombined chromosomal strands from each of the chromosome pairs. The results are embodied, *i.e.*, packaged, into haploid gametes, egg or sperm.

During the lifetime of a human male individual, it has been conservatively estimated that something on the order of 10^{12} sperm (a million times a million) can be produced (Levitan and Montague, 1977). We must also realize that in all probability no two of these male gametes is identical in genic content. This amazing result stems from the two aspects of chromosome behavior that are the heart of the recombination system: crossing-over between strands and then random segregation of the results into the nucleus of gametic cells.

Variation at the level of the population

In most genetic systems, the gametes do not genetically represent the next generation of individuals. The latter are produced by the coming together of two haploid gametes, usually from separate individuals, to form diploid zygotes. The reproducing individuals are each drawn separately from a population; this expands to a new level the intensity of genetic recombination. All of the processes in nature that bring the male and female gamete-bearers together are thus also part of the genetic system, since they act as determinants of which two gametes among millions of possibilities will actually unite.

Gametic union is far from the random

chance process that it might appear to be when we observe certain simple and familiar examples. Thus, it is possible to hormonally stimulate a female frog or toad to ovulate a mass of eggs at one time and then to artificially add spermatozoa to them in a dish, so that fertilization can occur. Shortly, this discussion will turn to the many factors that enter into the coming together of two members of the opposite sex in the final reproductive act related to genetic recombination. But first, let us consider the concept of variability at the population level.

So far we have dealt with the generation and fate of variability at the level of the *individual*. But in nature no individual exists alone: male and female alike are part of a larger biological community of individuals, the population. When male and female meet in reproduction they are performing the basic act imposed by the separateness of the individual. They provide fertilized eggs, zygotes, that grow into additional separate individuals in which crossing-over and random segregation can recur in the same manner as in the individuals that made up the previous generation.

As mentioned earlier, the mating system of a population more or less determines which individuals shall participate in the reproductive act and thus serve as a bridge into the hereditary material of the next generation. Accordingly, the complex sociobiology of sexual reproduction is a very important aspect of the genetic system. The ultimate recombinational event that occurs at syngamy and restores diploidy is often called "chance recombination." This latter phrase turns out to be somewhat of a misnomer since many inherited environmental influences are known that affect the choice of mate. The chance element exists but directed, genetically controlled processes also play a substantial role.

Under some circumstances, as when the population is small and local, the sexual partners may be genetically related to one another, a condition that is called inbreeding. In the opposite case, wherein the sexual partners come from distant subdivisions of the population, the mating is unlikely to be between close genetic relatives and so is referred to as an outcross. The study of inbreeding *versus* outbreeding forms an important part of the science of population genetics since continued inbreeding or outbreeding may be expected to have opposite effects on the store of genetic variability in a population. The former tends to restrict variability and the latter promotes it.

In a number of plants and animals, the genetic system has become genetically modified in such a way that inbreeding is prevented, minimized or by-passed. In some flowering plants, where self-fertilization (the ultimate in inbreeding) is possible, genetically-controlled self-sterility mechanisms often militate against such close inbreeding.

Avoidance of matings between close relatives is not the only type of non-random mating system that is known in natural populations. As Darwin argued extensively in his book *The Descent of Man* (1871), sexual selection exists widely in nature. Primarily involved are devices that promote the choice of high fitness mates. In some animals, intrasexual selection among males is common. Thus, males may battle, or subtly vie with one another in a manner that assures the winner a favored access to females. Thus, the sperm of some males are transmitted to the next generation and those of others are not. It is likely that there is a substantial genetic component in this process.

In many instances, the female, far from being passive, is able to reject or by-pass certain males in favor of others that apparently are perceived by them to be of superior fitness. Influences of this sort can have a powerful effect on the determination of the particular genes that are passed on to the next generation and those which are not. Recently, considerable emphasis has been given to comparable processes in plants (Willson and Burley, 1983) as well as in animals (Bateson, 1983).

Early in the study of the genetics of natural populations, balanced genetic polymorphism was discovered. Fisher (1930) was the first to point out that if the heterozygous individual is continually favored by selection, the result will be the permanent maintenance of the segregating variants in the population. Theoretically, they will be retained over an infinite number of generations. This is clearly a powerful force for the maintenance of genetic variability in populations. Such variants are said to be maintained by stabilizing (or balancing) selection. Another way to refer to this process is to emphasize the superior fitness of the heterozygote by referring to that individual as displaying heterosis or hybrid vigor. The vigor referred to in this connection is not necessarily that which merely permits the heterozygous individual to survive better. In order to have importance in populations, survival must be accompanied by superior reproductive ability.

The existence of balanced polymorphism is probably the best explanation for the consistent maintenance of the enormous amount of variability found to exist in populations. For example, populations of many species of *Drosophila* flies display inversion polymorphism. Every indication suggests that most of these inversions are held in the populations by balancing selection that favors the heterozygous state.

THE SPECIES AS A FIELD OF GENETIC VARIABILITY

The diploid cross-fertilizing gene system

From what has been outlined in the preceding section, it is clear that patterns of inheritance usually permit both the generation and maintenance of genetic variability. "Like produces like" is therefore true only in the broad sense. Thus, dogs always produce dogs but when each puppy produced by a pair of parent individuals is examined carefully, the existence of genetic variability is abundantly demonstrated.

Such variation appears to exist even within inbred lines produced by the animal or plant breeder. What appears to happen is that natural selection in later generations of these inbreds comes to oppose artificial selection by favoring the higher reproductive fitness of heterozygotes for blocks of genes. Thus, the move towards total homozygosity that simplistic application of inbreeding theory appears to require may be blocked more or less automatically in both artificial and, indeed, in natural inbreeding populations (Allard *et al.*, 1975).

The interbreeding group of individuals that we recognize as a species, especially when it exists in wild populations not being selected by man, represents a field of separate individuals manifesting genetic variability. The principal pattern of inheritance that promotes this variability is the diploid, sexually-reproducing genetic system. Restrictions on the power of this system to generate variability will be dealt with later. It is probably not a coincidence that the major organisms that have been used for experimental study of genetics all have a highly-developed recombinational system; all reveal substantial genetic variability, making them favorable for observing the laws of inheritance in general and genetic recombination in particular. I refer to the four "m's," man, mouse, maize and (*Drosophila*) *melanogaster*.

Despite the fact that the basic pattern of inheritance is the same in these widely different species, interesting variations occur. These will now be the subject of comments.

The genetics of man

There are many advantages to the study of genetic variation in the human species. One of them is the ease of intuitive observation of the differences among siblings in a family. Thus, the reality of the genetic uniqueness of each individual is easy to establish without complex screening methods. The observational process, however, is to a considerable degree hampered by the fact that almost every character of importance is also affected by the environment in which the individual exists. Some traits (*e.g.*, eye color) manifestly are little affected by environment, whereas others (*e.g.*, cognitive ability) are strongly affected by both heredity and environment. Thus both of these influences are important, but each trait has to be considered separately so that an estimation of the relative contributions of heredity and environment can be made. Although the technical study of important human characters requires a rigorous statistical approach, intuitive observations leave no doubt that heredity plays an important role in many diverse characters of the individual. As indicated earlier, the comparison of genetic systems is particularly pertinent with regard to variations in potential for gene recombination due to differences in three areas: the intensity of crossing-over, the extent of random segregation due to chromosome number, and variations in the nature of the mating system.

In the human species, genetic recombination is extremely high. For a diploid species, the chromosome number is large, consisting of 23 pairs (the 2n or diploid chromosome number is 46 in both sexes). The chromosomes synapse in pairs. Crossing-over sites are distributed throughout the length of each chromosome pair, that is, they are not localized to a particular point, a circumstance that, if it were present, would reduce the capacity for recombination. Random segregation of these scrambled chromosomal products occurs in the meiotic cells of both sexes. The one exception to free recombination is the XY chromosome pair in males. The Y chromosome, essential in its intact form for the determination of the male sex, does not effectively exchange material with the X chromosome. This circumstance reduces the number of freely recombining pairs to 22 in males. This is still a substantial chromosome number for a diploid.

If we make the almost absurdly conservative assumption that there are allelic differences at each of only two loci on each chromosome in an individual, crossing-over can still produce a very large number of different kinds of gametes. This number of gametic types is given by the formula 4^n, where n is the number of autosomal chromosomes. This amounts to 4^{22} or about 2×10^{13}; the female can produce even more (4^{23}). These figures are so large that intuition cannot help understand them. The human species, furthermore, is moderately outcrossed; this is the third recombinational factor in the system and leads to the release of variability at fertilization. It is likely that the early evolution of man occurred in small, semi-isolated bands of hunter-gatherers; these were often mobile clans. Later such groups tended to become stationary and develop a village structure. Modern urban societies are characterized by outbreeding as intermarriage among the clans and villages has occurred. This fact, coupled with the great size of the present human population means that some minute realization of the astronomical potential for genetic recombination has occurred and is occurring. Probably no other form of life in the history of the earth has ever undergone such a genetic release, even if its genetic system was competent to generate such variability.

The genetics of the mouse

Of all the experimental animals that have been developed, the ordinary house mouse *Mus musculus* has probably received the greatest attention. The human geneticist cannot plan and arrange particular crosses; he finds marriages and families as already accomplished facts and he must develop sensitive and unobtrusive methods for studying them. He is thus deprived of a most valuable tool for understanding the details of how particular traits are inherited. The mouse is a superlative laboratory mammal and a vast literature exists on its genetics, analysis of inbreeding effects and quantitative traits and the mapping of the chromosomes in exquisite cytological and molecular detail. The mouse is also a favorite object for research in developmental biology; modern methods include studying the relationship between mouse and human chromosomes in man-mouse hybrid cells in tissue culture and various nuclear and cell transplantations.

The mouse has a pattern of inheritance quite similar to that of man; having a slightly smaller diploid chromosome number. Crossing-over is free and extensive throughout the genome and, as one might expect, genetic variability due to recombinational events is very large. As measured by electrophoretic methods, raw levels of heterozygosity for loci encoding soluable proteins in natural populations are high, averaging about 9% as compared to about 7% in man. Recent studies of DNA variability, however, suggest that the true heterozygosity level is very much higher.

All this suggests that the mouse is correctly viewed as a good model by which to judge the pattern of inheritance in man. Both species show strong naturally-occurring variation among local, relatively inbred populations. In man, no alterations in chromosome number have become fixed in local populations and most geneticists have concluded that the human variation system reflects a single polytypic species. The human species was at an early stage subdivided into partially isolated geographical subspecies representing the early occupation of the major continental land masses. These isolated subpopulations have largely broken down by intercrossing, beginning several thousands of years B.C. and continuing to the present day.

In the mouse, the situation in natural populations is quite different. The common house-mouse subspecies (*Mus musculus domesticus*) has been distributed worldwide, mostly because of its commensalism with man. North-central Europe, however, appears to be the ancestral home of this mouse. Additionally, study of various natural populations, especially in the mountains of Italy, have revealed a number of populations with altered chromosome numbers; these are often accompanied by distinct phenotypic differentiation. Some of these populations have been accorded the rank of full species, especially in view of various naturally-occurring reductions in chromosome number. These result from fusion (by chromosomal translocation) of certain separate chromosome arms of the basic *Mus* karyotype. The most extreme of these reduces the number of segregating pairs in the chromosome set from 20 to 11. These animals still look and act like ordinary house mice. Populations having such conditions in fixed state have their recombination potential substantially lowered, since the number of independently assorting chromosomes at meiosis is reduced. As far as is known, however, crossing-over is not affected. A number of these variant mouse populations are rather small and inbred, a fact which further reduces their capacity for generating genetic variability by recombination.

The genetics of maize

The maize or corn plant (*Zea mays*) has long served as a prototype for plant genetics. Corn is diploid with 10 pairs of chromosomes. Lacking any chromosomal sex-determining system, all chromosomes show non-localized crossing-over. Although self-pollination is possible, the plant is normally outcrossed and substantial variability exists. The plant appears to have evolved from wild ancestors in tropical America, where it was originally brought into cultivation by American Indians. Hybridization appears to have been involved in its origin and this may be partially responsible for the wealth of genetic variability that has been available to breeders for use in programs of crop improvement.

The modern corn plant has a very inefficient means of dispersal, owing largely to many centuries of selection for a large-sized, nutritious grain. Corn is essentially a giant species of grass; like most grasses, it is wind pollinated, a process that also promotes outcrossing. The dispersal stage, the pollen grain, contains the gamete nuclei. As will be mentioned below, however, many grasses have greatly reduced recombination due to the frequent bypassing of the sexual process of apomixis or vegetative reproduction.

The genetics of melanogaster (Drosophila)

This famous organism has served the fundamental geneticist well. Methods have been developed for exquisite engineering of its hereditary material. Despite the fact that it is a fast-breeding insect and seems remote in nature from the other three organisms discussed, almost all important principles of the genetic system may be investigated in fine detail with the techniques of modern genetics.

Despite its wide usage, *melanogaster* has only four pairs of chromosomes and thus a comparatively restricted recombination index. Crossing-over is restricted to the female sex but is distributed along the length of the chromosomes. Nevertheless, one of the chromosome pairs is very short and, compared to the others, does not have many genes on it. Segregation is random in both sexes but the small chromosome number, lack of crossing-over in the male and the existence of the short chromosome all serve to reduce recombination. What is true of *melanogaster* is largely true for many other species of *Drosophila* although some have slightly higher chromosome numbers.

Restraints on recombination

Some of the examples discussed in the preceding section anticipate the general conditions that restrain recombination. Crossing-over may be restricted in a number of ways. In addition to those devices already mentioned, there may be strict localization of crossovers to a small region of the chromosome pair, as found in certain grasshoppers. In the bees and wasps, only the females are diploid; the males develop from unfertilized eggs and therefore are haploid, having only one set of chromosomes throughout their life. In this case, therefore, the male has a genetic composition that is equivalent to a gamete. Not only is there no crossing-over but no random assortment occurs. Thus, all of the recombination in these insects is confined to females.

The biological meaning of chromosome number, at least in diploids, appears to be related to recombination. In certain diploid animal and plant lineages, we find it possible to recognize a base number from which certain related species or species groups show some differences, apparently derived from the basic number. This latter number often appears to be a reduction: in a few cases, increases are known to occur. The latter, of course, would increase the recombination. These changes apparently arise by a selection process in natural populations; the various resulting chromosomal conditions are said to have been established through chromosomal or karyotype evolution.

Still another type of recombination-reducer may be recognized in natural populations. If the two homologues of a chromosome pair have the same gene order, crossing-over between these homologues is usually unimpaired. When one member of a pair has a section that differs in gene order from the other, recombination in this particular section is reduced. This type of chromosomal aberration, the inversion, is the common relevant type of mutation. An inversion arises in a normal, natural population and sometimes, rather than being eliminated, it increases in frequency, often until some selective forces tend to hold it within the population in a state of stable, balanced frequency. Inversion systems have been widely studied in various *Drosophila* species where their existence can be directly visualized in the giant chromosomes of the salivary gland cells.

From the point of view of the genetic system, the importance of natural inversions centers around the fact that they effectively prevent crossing-over within their confines. The group of genes included in that chromosome section is thus held together as a block. In the heterozygous individual, the inverted section and its counterpart interact so as to produce a fitness higher than either of the sections when homozygous. This leads to balanced chromosomal polymorphism, one of the apparent benefits of reduced recombination.

In a number of plants and a smaller number of animals, the basic chromosome number in a species may become doubled, a sort of mass chromosomal mutation based on either fusion of cells or by some sort of misdivision. This not only may occur naturally but can be induced by laboratory manipulations. Clearly natural polyploidy represents a major alteration of the genetic system. Space for this article is too limited to allow exploration of all the complexities of the cytogenetics of polyploids, but an outline of these effects can be given. When a polyploid arises within a population of a species (autopolyploidy), the presence of four homologous chromosomes rather than two is likely to cause difficulties of synapsis and segregation, since segregation from groups of three or four conjoined chromosomes is irregular. This gives rise to unbalanced gametes and sterility. Such polyploidy can persist for some time if the plant or animal is able to reproduce asexually or vegetatively. Indeed some sort of mechanism that bypasses sexual reproduction characterizes many polyploids.

The persistence of polyploids is also abetted by a superior vigor that they usually show. Apparently, the presence of four homologues tends to cover up deleterious recessives or somehow provides a more efficient hereditary background for biochemical pathways. Sexual reproduction in polyploids may be restored to efficiency by a process of selection for increased fertility extending over a number of generations. One result will be the restoration of synapsis of chromosomes in regular pairs. Such a polyploid will then be essentially re-converted to a diploid, but one that has an embellished chromosome number. As mutational variability accumulates, such diploidized polyploids may eventually become efficient engines for the generation of new recombinational variability.

Hybridization between species is not at all uncommon in nature. Plants, in particular, frequently form hybrids that are fertile, although under most circumstances hybrids are not as well adapted as the species from which they were formed. When a hybrid occurs between two quite dissimilar plants, there may be very little pairing among the chromosomes in the F_1, a condition that renders this hybrid quite sterile. Should polyploidy ensue, in a hybrid with such dissimilar chromosomes (allopolyploidy), a remarkable result is sometimes observed: the hybrid with the doubled chromosome number may now display a high degree of fertility, since chromosome pairs may be formed normally, quite unlike the condition observed in autopolyploidy.

In many forms, particularly in plants, polyploids of a higher order arise; often a doubling occurs in a cell that already has a chromosome number above the diploid level. These higher levels of polyploidy are frequently associated with an asexual means of reproduction and thus do not provide a further basis for increased genetic recombination.

SEVERELY RESTRICTED GENETIC SYSTEMS

A number of species in both plant and animal kingdoms have lost the meiotic system in both sexes so that they fail to retain both the capacity for genotypic renewal at each generation and the benefits of genetic recombination. The main result is that novel, progressive evolution ceases. They have essentially come to an equilibrium phase. Such species, whether they are diploid or polyploid, and despite their mode of chromosomal reduplication, nevertheless slowly accumulate minor genetic changes by mutation. Most of these are likely to be of individually small phenotypic effect since large changes would not be expected to integrate into the genome without the assistance of recombination. In other words, under the recombining system, selection is able to find, by trial and error, a compatible genetic milieu for the changed gene. In the absence of recombination, as in the present case, large changes are rarely observed and when they are, they appear to be accompanied by reduced fitness, so that long-term survival is likely to be limited.

Parthenogenetic reproduction, especially that which is known as thelytokous (females produce daughters only), usually involves the elimination of the male sex completely. Reproduction is taken over by the female so that the descendent lines bypass the fertilization phase. Effectively, this discards a large amount of the benefits of meiosis. In some cases, however, meiosis continues in the female during the production of the eggs. This permits some elimination of lethal genes and genes of deleterious effect in polar bodies.

When reduced to such systems as the foregoing, meiosis may retain a sort of cleansing effect on the genome but there would appear to be little opportunity for generating complex new adaptations or to produce new populations ultimately recognizable as descendent species. Indeed, such organisms are essentially invariable clones. Although they may persist for many generations, such biological entities appear to have modified the very genetic system that was instrumental in their establishing its genetic uniqueness in the first place.

Extreme inbreeding in a population is a condition that resembles the loss of meiosis and parthenogenesis, since it leads to genetic inflexibility. The same selective processes that favor inbreeding may sometimes lead to obligatory self-fertilization. Both male and female reproductive organs may be retained but that large component of recombination that depends on mate choice and obligatory outcrossing is discarded in favor of a process that tends to fix the genotype. Recombination-promoting conditions like self-incompatibility in plants or obligatory outcrossing methods (wind-pollination, for example) may be subverted to conditions that impose greater genetic stability.

The ultimate reduction in recombination is provided by a complete and total loss of all the processes related to sexual reproduction. Meiosis is aborted; the reproductive organs may be lost or subverted to conditions where mitosis supplants meiosis in the formation of reproductive cells. Reproduction occurs by a process of vegetative reproduction wherein the next "generation" is not a new generation at all but is reconstituted from an asexually produced group of cells. These will retain the same exact genotype as the parent plant. As the great genetical botanist Edgar Anderson used to put it, the offspring produced are merely "little bits of mother."

Conditions of this sort make sense from the evolutionary point of view if we remember that the adjustment to the environment may proceed via recombination and selection over thousands or even millions of generations. Slowly, a degree of perfection in the adaptation is attained such that any genetic improvement is likely to be very small indeed. The inevitable result of this may well be that the recombination system that was responsible for building the adaptation, now becomes a burden and is best dispensed with altogether. Groups that are very old from the phylogenetic point of view, like the "imperfect" bacteria and fungi, have no known sexual methods of reproduction. The most feasible interpretation of this condition is that they have lost them rather than never having had them initially. To progress from the evolutionary point of view, recombination is an essential ingredient of the genetic system.

GENETIC SYSTEMS AND EVOLUTIONARY CHANGE IN POPULATIONS

Constraints on the genetic system

The earlier sections of this article have stressed the role of the mutation and recombination in sexual populations and the role these processes play in providing a field of variability. The most important aspect of this is that this field of variability is directly expressed and encapsulated in the genotypes of individual organisms. You and I are both examples of such encapsulations. It is through the reproduction of these individuals that the process of selection operates. Just as the animal or plant breeder surveys the variability in his artificial populations and selects those from which he wishes to breed, so does this also occur naturally in natural populations. Selection processes of all sorts, of course, are effective in direct proportion to the richness of choice. Those individuals that reproduce best populate the succeeding generation. Nature's individuals that are comparable to the culls of the breeder are very simply those that have fewer offspring than the more successful.

What has been described in the foregoing paragraphs has been generally referred to as "Neodarwinian microevolution." The enormous power of selection derives directly from the ability of the genetic system to generate variability. Selection above the level of the species, for example, between groups of organisms or even species (see Stanley, 1975) is surely possible but it suffers a great reduction in effectiveness by lacking the key element, an exuberant field of variability.

The various genetic systems themselves appear to be the direct outcome of natural selection. Thus, modifications of chromosome number and behavior, self-fertilizing mechanisms, parthenogenesis and so forth arise as variants in populations. As genetic systems, they are increased and even fixed in populations by selection. We have come to think of natural selection as a process that adapts populations to simple ambient environmental facets, such as temperature, food sources, rainfall or soil type. Selection does these things, of course, but on the other hand it also tends to be extraordinarily opportunistic in that any variation serving immediate success in reproduction may be seized upon, and may increase in frequency. For example, one may see a parthenogenetic system easily become the object of positive selection under conditions wherein there is a chronic shortage of males in the population (see Stalker, 1954). Among the ordinary haploid eggs laid by an unfertilized female, a very few may by chance have the possibility of fusion between the definitive egg nucleus and one of the polar bodies that would be normally extruded from the egg. If this does occur, then the haploid chromosome number will become duplicated, permitting the egg to develop as long as it is not homozygous for lethals or some other deleterious genetic condition. The evolution of such a genetic system in the laboratory has been directly observed in artificial populations from which all fertile males have been excluded (see Carson, 1967).

A major contribution of Sewall Wright to evolutionary genetics is the stress placed by him on the interaction of the size of the population with the type of selection that is going on within it. These conclusions were first advanced in a 10-page 1932 article which has never been surpassed for clarity and incisiveness. When a large population becomes drastically reduced in size its carrying capacity for genetic variability is also reduced and sharp changes in the frequency of some genes and gene complexes occur. There is a strong element of chance involved in this loss of variability. Wright has referred to this process as "random drift" and has calculated some of the expected mathematical results. His most revealing calculations stress that it is the interaction of selection with drift that is important. Thus, in very large populations, selection is more important whereas in very small ones some chance events due to drift may be expected.

Adaptation and speciation

Evolution manifests itself in two ways: it produces adaptations and it produces species. In a number of instances in this article, stress has been placed on the abundance of genetic variability in sexually-reproducing and cross-fertilizing forms. Adaptation is a phyletic process: the whole population progresses genetically in a manner that progressively sharpens the adjustment to the relevant environmental conditions. The formation of new species (speciation) appears to require the sundering of a larger gene pool into one or more daughter populations that to some degree are out of genetic contact with the original population and each other. This isolation, whatever may be the initial cause, permits the formation of one or more groups of organisms that thereafter may follow independent genetic pathways down through the generations. Again, selection is the important process that assures that the populations become permanently different. If the diverging populations are in contact with one another, hybrids may occur but selection in two different directions may be so strong as to gradually eliminate cross-breeding. In fact, the populations may become reproductively isolated and so attain a permanent separate status. The pattern of inheritance, or what has been called here the genetic system, plays a very important role in the modus operandi of evolutionary processes.

TOWARDS A NEW SCIENCE: THE COMPARATIVE STUDY OF GENETIC SYSTEMS

The extraordinary diversity of living things has one common feature: each individual and species is encoded by its own unique DNA. Perhaps the most notable feature of this hereditary system is the ever changing nature of the DNA. The most remarkable living organisms, such as the human species, have this hereditary material organized into a sexually-reproducing, cross-fertilizing diploid system of inheritance. Clearly, the nature of the genetic system, including its freeness to vary and recombine, is a key feature of every species. Up to the present, geneticists have tended to be satisfied with a description of the major features of the genetic system. A new science that is emerging is the interpretation of the genetic part of a species by examining in detail the genetic system that it has at the present time level.

Certain groups of organisms, for example, tend to actively proliferate many new and unique species. In others, even some that seem to be very similar, this proliferation does not occur. One may hypothesize that a detailed understanding of the genetic systems of two such groups or organisms may indeed hold the keys to an understanding of why such variations in evolutionary pattern occur. Molecular and cytological methods are now available that can serve as methods of attack on this problem. Comparative studies of anatomy, physiology, biochemistry, geographical distribution and so forth have served biologists well over the past century. We now have the possibility of entering a new era of study that may enable us to establish a true science of comparative evolution.

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How Important is Genetics for an Understanding of Evolution?[1]

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Synopsis. The contributions of modern genetics to the understanding of evolution have been threefold. First, it has documented the extent of genetic variation that exists in populations as a basis for future evolution. In particular it has shown that natural selection has not destroyed all variation, as might be predicted, so that there must be mechanisms for the maintenance and origin of new selectable variation that balance the homogenizing forces of selection. Second, it has begun to provide a mechanism of the origin of genetic novelties which must be at the basis of the major features of the history of life. In doing so, it has shown how selection for new features is at all times historically contingent and that evolution is at all times at risk of falling into genetic dead-ends. Third, modern genetics has greatly enriched the diversity of mechanisms known to cause evolutionary change. All of these mechanisms involve the conversion of variation between individuals into variation between populations in time and space, but many are non-selective or even counter-selective. Natural selection is not the only mechanism of evolution.

INTRODUCTION

At first sight it seems absurd to ask about the contribution of genetics to our understanding of the evolutionary process. After all, it is obvious that neo-Darwinism is precisely the union of concepts from Mendelian genetics with the Darwinian theory of natural selection. The dependence of evolutionary explanations on basic principles of genetics is manifested by the demand that students study genetics before evolution, by the initial chapters on population genetics in textbooks of evolution (some of which turn out to be little more than an explanation of population genetic concepts), and by the great classics of evolutionary synthesis like Dobzhansky's *Genetics of the Origin of the Species* (1937) and Mayr's *Animal Species and Evolution* (1963). Evolution is "descent with modification" so the rules of descent are obviously at the basis of the rules of evolution. Indeed, we might go as far as Dobzhansky (1951) and say that "evolution is a change in the genetic composition of populations" and so conflate the study of evolution with the study of population genetics, pure and simple. Is there really any more to be said than is already packed into the intellectual baggage of any student of biology? The answer is, "Not much," if we restrict ourselves to the domain of evolutionary theory at its simplest level.

We all know, for example, that Mendelism saved Darwin's theory of evolution by natural selection from what appeared to be a fatal contradiction. Darwin's theory amounts to claiming that the differences that appear between populations and species in space and time are the concentrations of differences that already exist between individual organisms within populations. Natural selection (as well as other, non-selective population processes) causes an increase in the frequency of some heritable types in some populations as compared with other populations and so the populations diverge in their collective properties. Such a theory depends absolutely, then, on the existence of inter-individual variation as a condition of evolution. But theories of continuous blending inheritance predict that sexual reproduction will result in a homogenization of a population and a rapid loss of intra-population variation. In fact, the variance in a phenotypic character will decrease by a factor of ½ in each succeeding generation of blending. Thus, Darwin's theory, dependent as it is on standing variation, could not be right in a world of blending inheritance. Mendel's principle of segregation, as embodied in the Hardy-Weinberg equilibrium, its mathematical expression, guaranteed the maintenance of heritable variation despite the union of gametes from different parents.

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Unfortunately, although Mendelism saved Darwinism from sex, it could not save natural selection from itself. The problem of the modulation of variation by reproduction quite aside, evolution by natural selection is a self-negating and self-defeating process. Beginning with a population that has somehow acquired heritable variations in traits relevant to survival and reproduction, natural selection will cause an enrichment of those heritable phenotypes, "the fit," with the highest reproductive rates until the population consists only of these most fit types. That is, beginning with a heterogeneous assemblage of organisms, selection produces a homogeneous assemblage among whom there is nothing left to select. "Selection" on the one hand demands variants among which to select, and on the other hand disposes of variants, destroying the very fuel that drives the motor of evolution. If evolution is indeed "a change in gene frequencies of populations," then genetics must somehow show how continued change in gene frequencies has been possible over the last 2 billion years. And it is precisely this task that has been addressed by molecular, developmental and population genetics and which has been the great contribution of the science of genetics to evolutionary biology. That is, genetics has saved naive Darwinism, with its exclusive emphasis on selection driving populations to a fixed most fit type, from foundering on the rocks of its own contradictory formulation. It has done so by three paths:

1) Population and biometrical genetics has shown that, for whatever reason, there is considerable heritable variation in virtually any population, on which selection may act. That is, selection has not, in fact, exhausted variation.

2) Molecular and development genetics have elucidated how new heritable variation can arise, and can provide the basis for genetical novelties beyond the limits of variation that already exists, into the indefinite future.

3) Developmental and population genetics have vastly enriched our knowledge of the repertoire of evolutionary forces, beyond simple selection, to explain the diversity and continued diversification of organisms.

THE EXISTENCE OF DIVERSITY

The most direct evidence of the existence of heritable variation on which selection can operate has come from artificial selection experiments. The great mass of such experiments has been carried out in agriculturally important animals and plants, but these might be regarded as atypical in several respects. First, a rather limited range of traits has been selected, usually those directly concerned with yield of seed, milk, flesh, etc. that are of direct agronomic importance. Yet even these often involve complex physiological and anatomical changes that amount to remaking the organism. The selection for machine harvestable tomatoes required changing the growth habit of the plant, replacing indeterminate by determinate growth, making both flowering and fruit ripening virtually synchronous, changing the shape and texture of the fruit and the length of the growing season, among other traits. A more serious limitation on the generality of results from agronomic selection programs has been the previous breeding history of the stocks on which selection has been carried out. The population for selection has been sometimes derived from a closed flock or herd, in which case the genetic base is very restricted, sometimes from an historical variety in which case the original genetic variation is unknown, but most often from a deliberate cross between divergent populations in order to maximize the variation for selection. In any case, the relation to natural populations is doubtful. The outcome of such selection experiments is that almost always it is possible to make some progress, showing that there is heritable variation for a remarkable variety of phenotypic traits. It is the exceptions, however, that are most revealing for a general understanding of evolution. For example, there has been no real progress in breaking the "one egg a day" barrier in chickens, although there is plenty of genetic variation for egg production in poultry. Progress in selecting heat resistant varieties of cattle has also had indifferent success. Apparently, the complex physiological interactions that limit egg production to a daily rhythm, or that come together to provide high heat tolerance to productive cattle cannot easily be reorganized by mass selection directly on the trait itself. Some of this kind of limitation on natural selection comes from the very large number of so-far unbreakable genetic correlations between physiological traits in agronomically important organisms. So, for example, yield is negatively correlated with protein content in soybeans while nicotine content and carcinogenic tars are positively correlated in tobacco. These unbreakable correlations may represent purely historically contingent genetic correlations that might have turned out differently had the past history of selection and breeding been different, or they may be developmental and biochemical correlations that could not be broken by any constellation of genes that would still produce functioning organisms. In either case, they demonstrate the extremely important general evolutionary principle that despite heritable variation in separate characters in a population, selection may be unable to drive a response to some particular combination of character states. In this way correlated characters may resist selection and preserve variation that can be the subject of other selective forces at other times.

Artificial selection experiments on laboratory organisms derived from natural populations, chiefly various species of *Drosophila*, have shown unambiguously that extraordinary amounts of genetic variation for physiological and anatomical traits exist in nature. It is a commonplace of *Drosophila* geneticists that anything is selectable, from body size (Robertson and Reeves, 1952) through pattern of body parts (for example, Maynard Smith and Sondhi, 1960), to the amount of recombination in particular chromosome regions (Chinnici, 1971). From the mass of such experiments, the student of evolution is forced to conclude that heritable variation is present and selectable for a remarkable variety of anatomical and physiological properties. But not for all. Attempts to select for anatomical asymmetry in *Drosophila*, for example, have repeatedly failed to produce strains that are on the average larger on the left- or right-hand sides, despite the fact that individual flies are all slightly asymmetrical, but with no average right- or left-hand bias in the population as a whole. It is, however, possible to select for *fluctuating* asymmetry, that is for a population of flies each of whom is individually more asymmetrical, but again with no population bias toward right or left sides (Mather, 1953). This last case, is an example of an extremely important general result of selection experiments that is nevertheless misunderstood even by many geneticists. An organism is not determined by its genes, nor even by its genes and the environment in which it develops acting jointly, but by genes, environment, and random developmental factors acting at the level of single cell divisions and thermal noise. The left- and right-hand sides of a developing *Drosophila* are genetically identical, and, in any conventional meaning of the word "environment," have experienced the same sequence of developmental environments. Yet the left- and right-hand side of a fly will have different bristle numbers, different eye facet numbers and slightly different wing lengths. These differences have arisen by "developmental noise" during cell division and cell differentiation. There are then three distinct levels at which phenotypic variation occurs. First, in a fixed environment, or on the average over some specified distribution of environments, groups of organisms may differ in the average value of a trait because the groups differ genetically. Second, even if organisms have the same phenotype when exposed to a given developmental environment, they may differ in another environment. Moreover, heritable differences between organisms in one environment may be completely reversed in other environments. (See, for example, Gupta and Lewontin, 1982.) Finally, there is variation in the stability of developing organisms to microscopic perturbations in development during cell divisions and the growth and development of single cells and patches of tissue. What is significant for the understanding of evolutionary processes is that all three levels may be influenced by different sets of genes and may be subject to natural selection separately. That is, we may select to increase say, the average eye size of *Drosophila* at a given temperature; we can independently select eye size to have a greater or smaller response to developmental temperature (Waddington, 1960) and we can also select for lesser or greater individual fluctuating asymmetry at a given temperature (Mather, 1953). Natural selection can act on the average expression of a trait, on the responsiveness of the trait to changing environments, and on the internal developmental stability of a trait.

We must continue to bear in mind that most of the traits successfully selected for have been developmentally homogeneous and restricted, as for example eye facet number or the number of bristles on a particular region of the cuticle. Thus, a few genes or even a single segregating locus may contribute most of the genetic variation. More developmentally complex or generalized characters are not easily selected and may, as previously discussed, have unbreakable genetic correlations or else may not be under genetic control at all. So, although it is possible to select, independently, for greater and lesser developmental stability of eye size and wing variation in *Drosophila*, there are no genes for *general* developmental stability that effect both systems simultaneously (Scharloo, 1964; Lewontin, unpublished).

One of the most puzzling features of the observed diversity of organisms is the frequent contrast between the phenotypic homogeneity within groups and the diversity between groups. A good deal of the practice of systematics depends on the ability to make absolute distinctions between species, genes, or families, based on characters that are invariant within the group. Thus, a diagnostic character for the family Drosophilidae, as opposed to other families of Acalyptratae, is the presence of one proclinate and two reclinate orbital bristles. Every individual of every species of the family possesses this character, unlike all individuals of every species of, say, *Dacus* (the med fly) lacks it. In a theory of evolution that depends upon variation within populations for the source of variation between species, how do we account for these phenotypically constant traits? Are those traits never again to be the basis of future evolution, since they are now without selectable variation? One possibility, of course, is that there was once genetic variation for these characters, but that this variation was lost during the process of species differentiation and has not yet been recovered within species. Undoubtedly such purely historical explanations must be correct sometimes. The present environments of the species may select against intraspecific variations, whereas at a former time mutational variation was tolerated, and so, accumulated. Such hypotheses are, alas, unverifiable in particular cases. There is, however, another explanation for phenotypic uniformity, which has been uncovered by selection experiments, and which provides a very different insight into the possibilities of future evolution. This is the phenomenon of *canalization*.

All individuals of all species of *Drosophila* have two large anterior and two large posterior bristles on the scutellum. Using a mutation to disrupt the development of bristles, flies can be produced that have 0, 1 or 2 bristles instead of four. The average number of bristles in the mutant flies can be increased by selection so that 3 and then 4 bristle flies will appear. At the same time, among non-mutant sibs of the 4 bristle flies, some flies with 5 bristles will appear. There is now phenotypic variation in scutellar bristle number among non-mutant flies and this variation can be made use of to select 6, 7, 8 . . . bristle flies. So, apparently all the while there was selectable *genotypic* variation for bristle number, when there was *phenotypic* uniformity (see Rendel [1967] for his summary of these and similar experiments). The phenomenon of developmental constancy, despite genotypic (or environmental) variation, called *canalization* by Waddington (1942), is itself the consequence of genes for developmental buffering. These genes themselves are varying in populations and can be selected so as to increase or decrease the intensity of canalization (Rendel, 1967). Developmental buffering is not unlimited in its range. If a sufficiently strong perturbation of development occurs, either because a new mutant gene has drastically interfered with the developmental process, or because a major shift in environment has occurred, then the genetic variation for the trait will become manifest as phenotypic variation and natural selection may operate. Evolution of an apparently constant trait may then occur episodically as major environmental or genetic shifts occur, revealing the underlying genetic variation that was all the while present.

While selection experiments have revealed a fund of heritable variation present in natural populations, the description of that variation in genetic terms has not been possible because of the complex relations between phenotype and genotype. We cannot know from such experiments, for example, whether there are many segregating genes or only a few and whether there are many alternate alleles at these loci, or at what frequencies they are. Answers to these questions are important to the evolutionist because they provide knowledge of the long term prospect for selection, as opposed to the immediate rate of response revealed in selection experiments. Some information about the variation of single genes in populations has existed for a long time, chiefly genes whose products could be detected immunologically, as for example the blood groups in humans and cattle. Unfortunately, only genes that were already known to be variable could be studied in this way, so that no one can say how many red cell antigens are, in fact, invariant in populations. The gene-by-gene study of variation in natural populations was greatly enhanced by the introduction of protein gel electrophoresis into evolutionary studies (Harris, 1966; Hubby and Lewontin, 1966). This technique has made it possible, over the last 20 years, to study scores of gene loci (more than 100 in humans) in hundreds of species. Not all classes of genes are equally represented in these studies which have, for purely technical reasons, concentrated on soluble proteins, mostly enzymes, while finding out much less about membrane proteins, particle-bound enzymes and other classes of insoluble polypeptides. Unfortunately, no satisfactory method yet exists for a study of these latter, nor do we know what fraction of the genome they represent. When gel-electrophoresis was first introduced it was thought that only a fraction, perhaps about one-third, of the amino acid variation in proteins could be detected, since electrophoresis depends upon charge differences in proteins to discriminate them. Advances in technique (Singh *et al.*, 1976) and reconstruction experiments in which proteins of known amino acid composition and three-dimensional structure were subject to electrophoresis (Ramshaw *et al.*, 1979) have shown that their early doubts were exaggerated. For the most part, genes shown to be monomorphic or polymorphic with only two or three alleles segregating in populations, by earlier cruder methods, have proven to be accurately described. A few genes with larger numbers of segregating alleles like *xanthene, dehydrogenase* and *esterase* in *Drosophila*, are now known to be vastly more polymorphic than originally thought, with as many as 33 alleles segregating in a single population (Keith, 1983; Keith *et al.*, 1985), but these appear to be an unusually highly polymorphic class. As a consequence of the vast effort of evolutionary geneticists studying genic variation in plants, animals, vertebrates, invertebrates, prokaryotes and eukaryotes, it is now possible to make some strong generalizations about genic variation in natural populations. About ⅓ of all loci (based largely on loci coding for soluble proteins) are polymorphic in a typical species while ⅔ have essentially only a single allele characterizing the entire species. Of course, all loci have occasional mutations, but these rare events are not counted as making a locus polymorphic. Characterized in another way, in a typical diploid individual about 10% of its genome is heterozygous, while another 20% is homozygous for alleles that are varying within the species but happen to be homozygous in the individual. Thus, a typical *Drosophila* species would be polymorphic for, say, 3,000 loci, and typical individual fly heterozygous at 1,000 loci, if there are on the order of 10,000 genes coding for soluble proteins.

If the various alleles at each of these polymorphic loci were sufficiently different in their biochemical properties and activity to be reflected in the physiology and development of the whole organism, then we would be certain that an immense fund of selectable genetic variation was, in fact, present in nearly all species and that for some reason, the previous history of selection had not resulted in a genetically homogeneous collection as might be expected from simple theory. But we cannot be sure that all this genetic diversity is indeed physiologically important. It may turn out that many of the variant alleles in natural populations are functionally equivalent, at least at the level of the integrated physiology of the whole organism, so that species are indeed rather homogeneous from the standpoint of natural selection. That does not mean that the species could not *evolve*, but that molecular evolution would consist largely of the accidental and random replacement of one molecular form with a functionally equivalent one. Thus the molecular description would evolve, but not the function. It may indeed be that many of the amino acid replacements that have occurred in the evolution of molecules like cytochrome-c or haemoglobin over hundreds of millions of years are precisely of this nature. We appear then to be in a quandary. The purpose of studying molecular variation in natural populations was to determine whether, in fact, there is enough genetic variation for natural selection to continue to act whenever circumstances of life change, or whether selection exhausts relevant variation so that adaptive evolution is stalled for long periods for lack of something to select. The study has shown that a lot of genetic variation exists, but, in itself, the observation of that variation is insufficient to determine its possible significance to natural selection.

Most attempts to resolve this problem in the past have concentrated on detecting the action of natural selection in one of two ways. The first has been to make theoretical predictions about the statistics of genetic variation: how many alleles, their frequencies, the differences in their frequencies from population to population. These models are based both on selective and non-selective theories of genetic variation, in the hope that the actual data would discriminate between the models. These attempts have failed. Given the known processes of mutation, migration, fluctuations in population size, and varying kinds of natural selection, there are simply too many undetermined parameters to allow the theories to be rigorously tested. The second approach has been to try to measure directly the physiological or fitness differences between different genotypes. While some biochemical and physiological differences have indeed been detected in a few cases, of which alcohol dehydrogenase in *Drosophila* is the best documented (see Lewontin [1985] for a review), it has not in general been possible to measure the selective differences since, if they exist, they will be small.

A quite different way to resolve the problem appears if we consider the *monomorphic* rather than the polymorphic loci, or, what is equivalent, if we look within the allelic classes of the polymorphic genes. If a locus is monomorphic because selection is enforcing a homogeneity of amino acid sequence for functional reasons, then alleles that are identical in *kind* will not necessarily be identical in *ancestry*, at least in the recent past. On the other hand, if the monomorphism is purely a historical accident of the loss of new, functionally equivalent mutations through the inbreeding that occurs in finite populations, then we should expect all the alleles identical by kind also to be identical by ancestry. They will all be descended from a recent common ancestral gene in a common ancestor. But how can we distinguish between identity by kind and identity by historical descent if the genes are identical? By looking at their DNA sequences. Because the genetic code is degenerate there are multiple codons, usually differing in their third positions, that specify the same amino acid. If a locus is homozygous by selective constraint we should expect to see mutational variation in third positions (and in introns) despite homogeneity in amino acid sequence. If, on the other hand, the monomorphism is the result of recent common ancestry, then the third positions and introns will also be monomorphic in the population. The first such comparison of silent DNA polymorphism with amino acid polymorphism has been made for the alcohol dehydrogenase gene in *Drosophila melanogaster* by Kreitman (1983). In a sample of genomes taken from a geographical range including Africa, Europe, Japan, and North America, Kreitman found a 7% polymorphism of DNA bases in introns and third positions, but absolutely no variation in amino acids except for the single major two-allele electrophoretic polymorphism already known. Within the electrophoretic alleles there was complete uniformity of amino acids but a high level of silent base variation. Since ¾ of all random DNA base changes should cause an amino acid change, yet none were found, the evidence for consistent selection against amino acid substitutions is overwhelming. The monomorphism is a selective not a historical one. This makes it somewhat more likely that the single amino acid polymorphism that is observed is maintained by some sort of balance of forces, but the case is not proved and we might equally hold that it is the single variant that is tolerated by an otherwise very discriminating selection. The ability to distinguish historical from selective identity is a unique feature of studies of DNA variation and for this reason it is studies at this level which represent the future of experimental population genetics.

THE ORIGIN OF NOVELTY

Evolution cannot simply be the replacement of one variant allele at a locus by another. The major features of evolution involve the acquisition of new repertoires of biochemical, anatomical and behavioral traits that are often added to, rather than the simple replacement of alternative forms. A satisfactory Darwinism must therefore be more than the population genetics of shuffling old variation. It must include the phenomenon of genetic novelty. While this has not been a major theme of evolutionary genetics, a number of very illuminating discoveries have been made by molecular geneticists that mark out the territory for what must eventually become a major preoccupation of genetics and evolution.

A major advance in our understanding of the acquisition of new function has come from the study of the human globin gene family. Adult human hemoglobin consists almost entirely of a tetramer of two alpha chains and two beta chains. These four chains with their four haem groups form a structurally flexible unit that changes its shape during oxygenation and makes possible the cooperative effect that allows each added oxygen to attach more easily than the one before. The genes that code for the alpha and beta chains are on separate chromosomes, but when the amino acid sequences of the chains are compared they are essentially the same length (141 amino acids in alpha and 146 in beta) and are identical in 62 amino acids, more similar than human beta hemoglobin is to that of the shark. It is clear that the differentiation of alpha and beta chains arose by a duplication of genes, probably around the time of origin of the bony fishes. This duplication made possible the heterodimeric hemoglobin molecule with it's greatly increased efficiency of function. But that is only the beginning of the story. In addition to the alpha and beta chains, four other globin chains, delta, gamma, epsilon, and zeta appear and disappear during development. The delta, gamma, and epsilon chains differ from beta by only 10, 39 and 36 amino acids, respectively. Moreover, the genes for epsilon, gamma, delta and beta have very similar exon-intron structure and are arranged along chromosome 11 in the order within an extremely short distance of each other (about 50 kilobases). Clearly, this subfamily of genes has been derived one from another by gene duplication with some divergence. In like manner the alpha subfamily consists of genes all in a 40 kilobase region of chromosome 16. What is remarkable about those two subfamilies of genes is that their arrangement along the chromosome exactly parallels their appearance and disappearance in development. Embryos begin life with zeta and epsilon as the alpha-like beta-like components of their hemoglobin. Those then give way to alpha and gamma, making foetal hemoglobin, which then become, postnatally alpha and beta with small amount of delta. Presumably the four different hemoglobin tetramers that are produced at different development stages correspond to physiological exigencies of each stage. We see then that a differentiation and multiplication of function can arise by gene duplication followed by gene differentiation. That this differentiation sometimes goes awry is shown by the presence within both the alpha and beta gene clusters of pseudogenes, DNA sequences almost identical with the other of the family, but with fatal stop-code mutations that prevent them from coding proteins.

Another source of genetic novelty may be the conversion of a gene of redundant function to a totally new activity. Such a conversion has been demonstrated experimentally by Hall (1978) using the *ebg* gene in *E. coli.* This gene is induced by lactose but its enzyme has a low activity on lactose so its function in wild-type *E. coli* is unclear, but definitely expendable. Hall attempted to select mutants of this gene that would ferment a new substrate, *lactobionate.* He succeeded, but the order of events was extremely instructive. First, it was necessary to obtain a constitutive mutant, since lactose would not be available as an inducer. This regulatory mutation, a separate event, is a necessary first step. Second, direct selection with lactobionate produced nothing. It was necessary to build up the new function in three successive selections. First selection with lactose produced lactose fermenters. Some of these (Class II) were also fermenters of a related sugar lactulose while others were not (Class I). When Class I and Class II were selected with lactobionate again there was no success. When original strains were directly selected with lactulose, a positive strain (Class II) was produced, but this could not be further evolved to lactobionate fermentation. The *only* evolutionary pathway that succeeded was first selection with lactose to produce Class I, followed by selection with lactulose to produce Class IV, followed by selection with lactobionate to produce the final result. All other pathways and shortcuts were dead-ends. We see then that four separate mutational events (including the regulatory mutation) must succeed each other in the correct order and that other orders although they produce *phenotypically* intermediate stages in the evolution, are *genetically cul-de-sacs.* Evolving a new function is like threading a maze and temporary forward progress may be at the expense of eventual success. Evolution is an historically contingent process which does not allow any form to arise from any other. The structure of accessibility in evolution reflects in part the history of particular mutations that have occurred historically. What Hall's experiment shows is that evolution consists not only of opening new possibilities but of closing off others at the same time.

Alternatives to Adaptive Selection

The earliest contribution of genetics to evolutionary theory was to show, both theoretically and experimentally that natural selection of small variations in phenotype could explain continued evolution, as Darwin claimed. This was, in fact, the burden of Fisher's *Genetical Theory of Natural Selection* (1930) and Haldane's *Causes of Evolution* (1931). The irony is that the development of population genetics since that time has shown that while direct natural selection of character states may be a *sufficient* explanation of evolution, it is *not a necessary* one and that many other forces and phenomena are causes of evolution.

First, random historical forces may operate independently of or even contrary to selection. As shown by Wright (1932), in a finite population alleles with no selective advantage will be fixed by random drift causing random differentiation in space and time. Even *deleterious* genes can be fixed provided the product of N, the effective population size and S, the selective disadvantage are of order 1 or less. Moreover, new mutations are almost always immediately lost to the population even when they are selectively advantageous. The probability of the eventual incorporation of new mutation is only 2S, where S is the selective advantage of that mutation. Of course, if the same mutation occurs over and over again it may expect to succeed. But the time and population available are not infinite and many favorable mutations will fail.

Second, random factors may interact with selection to produce non-selective differentiation. Wright's models of adaptive peaks (1931) show that if genes interact epistatically in development there may be multiple stable outcomes to the same selective process. Which of these outcomes will be realized by a particular population depends upon chance fluctuations in gene frequency. As a result two populations may be driven apart phenotypically by natural selection even though they are both responding to identical selective forces. Selective differentiation does not mean differentiation of selection.

Third, the structures of inheritance themselves may drive genes non-selectively. The organization of genes on chromosomes means that if a locus is under selection and allele frequencies are changing, alleles at other loci, linked to the first but not under direct selection, will also evolve by the phenomenon of "genetic hitch-hiking." This linkage effect may cause pseudo-selective changes in totally unselected genes or counter-selective changes in weakly selected genes. The organization of genes on chromosomes also means that any abnormality in the process of chromosome replication or segregation will drive gene frequencies or that chromosome. Meiotic drive, in which chromosomes that carry a particular allele or chromosome segment are preferentially included in gametes, is a powerful mechanism for changing the frequencies of whole suites of unselected characters.

Fourth, genes have multiple developmental effects so that selection of one effect may cause unselected or even counter-selective changes in others. Eye pigments are probably under selection in *Drosophila*, at least in part for mating success. The same pigments are deposited in the Malpighian tubules, but these are never observed by any sensory apparatus. Not only genes, but all physical events have multiple effects. Selection has provided us with hemoglobin to carry oxygen. Our blood is red by physical accident and some animals have green blood if they have a copper haem pigment. Only in a trivial sense has selection made our blood red, an epiphenomenon of iron porphyrin structure. In addition, of course, there are the negative developmental correlations that arise from the pleiotropic actions of genes and which are then unbreakable in the absence of quite new kinds of mutations or drastic reconstruction of development.

Thus, the findings of developmental and population genetics have not simply confirmed the possibility of evolution of new species by the selection of heritable variants, the core of 19th century Darwinism, but have given rise to a vastly enriched 20th century neo-Darwinism which still understands the origin of taxonomic diversity as being rooted in individual variability, but which greatly extends the complexity of that process.

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Genetics of Crop Improvement[1]

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SYNOPSIS. Man has been engaged in the genetic manipulation of crop plants for millennia. At its most elemental level, plant genetic manipulation has three requirements: (1) a source of genetic variability that can be utilized for plant improvement; (2) methods for propagating desirable plant genotypes; and (3) strategies for the transfer and selection of useful genes or gene combinations. The modern science of genetics has provided many new approaches to each of these three aspects of plant improvement. Modern plant genetics has also led to a variety of environmental, political and economic problems. These problems include the loss of valuable plant genetic resources, the widespread adoption of monocultures that may be unstable in the face of pathogen epidemics, and the current political debates concerning the regulation and environmental implications of plant genetic engineering. It is impossible to judge these and related issues without a basic understanding of the ways in which genetics is applied in improving crop plants. The goal of this article is to provide an account of the applications of plant genetics in crop improvement.

INTRODUCTION

Genetics courses in American colleges and universities concentrate on the principles of genetic transmission and on the mechanisms of gene expression, but they rarely deal in any depth with the applications of genetics in agriculture or in medicine. This neglect of applications is also a general characteristic of elementary textbooks and courses in the biological sciences. Perhaps this situation has arisen because the applications of biology and genetics tend to require more advanced and specialized knowledge. Genetics is applied to problems in the agricultural sciences that seem arcane to the nonspecialist. Nevertheless, the applications of genetics in plant improvement have contributed to a profound change in U.S. agriculture over the past 70 years. We have introduced crop monocultures over large areas that are high yielding but genetically vulnerable to disease outbreaks. We have bred crops to suit our high technology and energy consumptive production practices. In the process, we have increased the productivity of the average American farmer several fold, and we have contributed to a major population shift from a rural to an urban setting.

If our accomplishments over the past half century seem awesome then what can we expect in the future? During the past five years many claims have been made about biotechnology and its potential impact on agriculture and food production. We are now on the threshold of using recombinant DNA technology to genetically modify plants and their associated microbial and pathogen communities for agricultural purposes. This potential has stimulated a national debate about the environmental consequences of the field testing and release of genetically modified organisms. The debate is being carried out in the courts, between potential government regulatory agencies (principally the USDA and the EPA), in the popular press and in the scientific community. The resolution of this debate may have substantial economic and environmental consequences, yet it is impossible to evaluate these issues without a basic understanding of the methods and principles of genetics as applied to crop improvement. The goal of this essay is to provide a brief account of the principles of plant breeding including the potential uses of molecular genetics in plant improvement.

THE DOMESTICATION AND GENETIC MANIPULATION OF CROP PLANTS BY PRIMITIVE MAN

In the current atmosphere charged with excitement about the economic potential of biotechnology, it is easy to lose sight of the fact that the first masters of biotechnology were neolithic peoples who learned to domesticate and modify plants for human exploitation. Virtually all of our major crop plants were domesticated by primitive man and our complex modern economies rest on the remarkable accomplishments of these early "genetic engineers."

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The origins of Old World agriculture began more than 10,000 years ago in the Near East. Our knowledge of this phase of human history is shrouded in uncertainty, based as it is on fragmentary biological and archaeological evidence. Still, it is interesting to note that the origins of Old World agriculture coincided with the end of the European Ice Age; perhaps the associated changes forced neolithic man to develop alternate food sources (Ucko and Dimbleby, 1969). Whatever the stimulus to the development of agriculture, it is remarkable that different plants were domesticated in a variety of geographic centers throughout the world. The question of whether these represent independent episodes of plant domestication by different primitive cultures is a subject of dispute (Darlington, 1969). Setting aside the independent invention issue, it is noteworthy that wheat, barley, peas and lentils were domesticated in the Fertile Crescent of the Near East, maize and beans came into cultivation in Mesoamerica, rice in Southeast Asia, and pearl millet and the sorghums in Africa (Harlan, 1975). Around 6,000 years ago fruit crops (olives, dates, grapes and figs) appeared in a second episode of domestication in the Mediterranean basin (Zohary and Spiegel-Roy, 1975). Having acquired the ability to domesticate and genetically alter plants, neolithic man seems to have applied this technology with a vengeance.

Primitive agriculturalists did not know the principles of modern genetics; they did what came naturally. They selected desirable phenotypes for propagation in the next generation. The result of this process of selection, repeated generation after generation for millennia, was the genetic alteration of the target population. We can analyze these differences when cultivated plants can be compared to their wild progenitors. In the case of wild barley (*Hordeum spontaneum*) the spikes (the inflorescence) become brittle and fall to the ground at maturity (the plants are said to shatter their seed), in contrast to cultivated barley (*H. vulgare*) which retains its spikes at maturity. This brittle (shattering) trait facilitates seed dispersal which is adaptively important in the uncertain environments occupied by wild barley. On the other hand the tendency to shatter makes the seed more difficult to harvest, because one must collect the seed in the brief period of time between seed maturity and shattering. Consequently the shattering trait is poorly adapted to agriculture.

Neolithic hunter-gatherers collected seed as a food source. If genetic variation existed in wild barley populations for the shattering trait so that some plants had less brittle spikes and retained their seed longer after maturity, it would be easier to collect seed from these plants, which would in turn contribute a disproportionate share of seed to the pool of collected seed. When neolithic peoples began to experiment with the cultivation of barley by sowing a portion of their collected seed, the nonshattering type would contribute relatively more seed to the next generation. As a result Neolithic man practiced a strong form of selection, albeit unconsciously (Zohary, 1969). He did not, after all, follow a deliberate plan for the genetic modification of barley. This process of unconscious selection explains how primitive man brought about major genetic changes in a wide variety of plants.

The barley example just discussed illustrates the following basic principles of plant breeding:

1. There must be a source of heritable variation for the phenotypic trait to be altered.
2. It must be possible to select for the trait to increase its representation in the next generation.
3. It should ultimately be possible to "fix" the desirable trait in all individuals in the population.

The remainder of this essay will develop some of the methods and strategies used to achieve these three objectives.

SOURCES OF GENETIC VARIATION

There is an inherent contradiction in the set of principles listed above. Useful genetic variants must be available for breeding progress, but the aim of the plant breeder is to fix a particular variant phenotype in the population, thereby purging the population of all other genetic variants affecting the phenotype of interest. The end result of this effort is the creation of genetically uniform populations. Indeed, modern agriculture is dominated by monocultures of single plant genotypes, grown over vast areas. In many instances these monocultures have supplanted the genetically diverse land races from which they were derived, and in so doing have eroded the reservoir of genetic diversity available to the plant breeder. Monocultures also have the undesirable feature of being vulnerable to catastrophic loss from disease or pest outbreaks. Dramatic examples of catastrophic loss can be found in the 1970 corn leaf blight epidemic in the U.S., or the even more famous Irish potato famine of the 1840s.

Germplasm conservation programs

During the 1960s the Food and Agriculture Organization (FAO) of the United Nations took a leading role in encouraging the collection and preservation of "plant genetic resources," a term coined by Frankel and Bennet [1970] and broadly construed to be the genetic diversity in cultivated and wild forms of economically useful plants. Ten years ago the International Board for Plant Genetic Resources (IBPGR) was established to coordinate the collection and evaluation of plant germplasm on a worldwide scale. In the United States, the USDA maintains a World Collection of plant materials and a National Seed Storage Laboratory (part of the National Plant Germplasm System) as a source of plant germplasm. This collection is generally felt to be inadequate, due to a history of inadequate funding by Congress and the USDA. Very recently the collection of genetic resources has emerged as a serious point of contention between third world and developed nations (see for example, *Diversity*, Vol. 7, 1985). The controversy arises from the fear of less developed countries that their plant genetic resources will be exploited by the developed countries and by international seed companies, without benefit to the country of origin.

The first task faced by the plant breeder is to evaluate sources of germplasm for the presence of the sought after phenotype. It is difficult to evaluate plant collections for genes and phenotypes that may have future value, since these qualities are unknown and frequently unpredictable. The best that can be done is to ensure that a wide sample of genetic diversity has been obtained. In this regard isozyme markers may be particularly useful (Brown and Clegg, 1983). The many problems associated with defining and implementing optimum sampling strategies for plant genetic conservation are discussed by Marshall and Brown (1975).

Table 1 lists sources of genetic variation potentially available to the plant breeder. Aside from germplasm collections and the wild relatives of crop plants, the breeder can attempt to transfer genes from other taxa. Interspecific hybridization may sometimes permit the utilization of useful variants, when reproductive barriers can be overcome. Embryo rescue techniques and plant tissue culture are proving particularly useful in this regard. Plant transformation, using the Ti plasmid and recombinant DNA molecules, is now beginning to be used to transfer genes between plants and other organisms as distant as yeast (discussed below). It is only a matter of time before animal genes are also transformed into plant lineages.

Mutagenesis as a source of genetic variants

Various mutagenic agents have been used to generate genetic variation *de novo.* This approach is appealing because one can attempt to produce useful variants in adapted cultivars without utilizing un-

TABLE 1. *Sources of genetic variation.*

Source
Germplasm collection
Wild relatives
Other taxa
Mutagenesis
Somaclonal variation
Synthesis of new genes

adapted germplasm. For instance, the gene for a semidwarf phenotype in rice was obtained following irradiation of the tall rice cultivar, Calrose (Rutger, 1983). The semidwarf phenotype shows enhanced yields under increased nitrogen fertilizers without lodging problems (lodging is a condition where the stem breaks or bends to the ground preventing harvesting of the grain). This gene has now been incorporated into a number of rice cultivars that are grown on 245,000 ha in California. Rutger (1983) also lists other useful mutants obtained from mutagenesis of rice, including genes for early maturity, waxy endosperm, and male sterility.

Mutagenesis does have several limitations. These include the fact that most mutants are deleterious and mutations are produced at random loci. As a consequence, deleterious mutations will arise at loci scattered throughout the genome. The utility of mutagenesis also rests on the ease with which large numbers of plants can be screened for the phenotype of interest. Even with the use of powerful mutagens, the per locus rate of mutation is small and thousands of individuals may need to be screened. If the screening procedure involves a complicated assay (*e.g.*, a biochemical assay), it may not be possible to implement the assay on a sufficiently large scale.

Somaclonal variation

It has recently been noted that tissue culture conditions induce high rates of mutation for morphological and biochemical phenotypes. This variation is termed somaclonal variation because it arises *de novo* in clonally propagated cell or tissue culture lineages (Larkin and Scowcroft, 1981). The molecular mechanisms responsible for the generation of somaclonal variation are not understood, but often seem to involve chromosomal rearrangements. Regardless of the cause of this variation, plant geneticists have been quick to seize upon the phenomenon of somaclonal variation as a means of obtaining genetic variants.

Synthesis of novel genes

At some point it will be possible to synthesize desired genetic variants and to transform these into the target plant. The synthesis of short DNA molecules is now routine. However, basic knowledge about the kinds of interactions that occur between DNA and proteins, or other molecules that regulate gene expression, is still very incomplete. This gap in our knowledge makes the *a priori* design of novel synthetic genes difficult or impossible. In addition, our understanding of the relationship between primary amino acid structure and enzymatic or other biological activity is not at a predictive stage. Finally, we may not be able to predict how a particular genetic variant will behave in the context of the functioning organism. Ultimately the novel gene must function in the context of the metabolic and developmental organization of the whole organism. All of these factors currently limit the utility of synthesized genes as a source of novel genetic variants.

THE PROPAGATION OF USEFUL GENOTYPES

It is not enough to obtain a useful phenotype; the genotype that specifies the useful phenotype must be propagated to future generations. At this point we have to consider transmission genetics and the complications of recombination in diploid or polyploid systems. We must also consider plant mating systems and systems of asexual reproduction. The simplest situation is the asexual propagation of a mutant genotype. Occasionally a somatic mutant (called a sport) is observed to differentiate a single branch of a tree from the remaining branches for some character. If the new mutant can be propagated asexually, then the complications of genetic segregation and recombination can be avoided and all asexual progeny will be identical to their parent. This describes the situation with many important fruit crops that are propagated asexually, including oranges, grapes, avocados, bananas and apples.

Asexual propagation of plant genotypes

Since I am from Riverside, California, it is natural to use the navel orange as an illustration of the asexual propagation of a desirable genotype. The navel orange is propagated by grafting a bud from the selected plant to a separate (genetically distinct) rootstock. (Rootstocks are often selected for disease resistance characteristics.) The navel orange is a sterile triploid and is thought to have originated as a sport in Bahia, Brazil. McPhee (1966) describes the history of the navel orange as follows: "In 1870, an American Presbyterian missionary in Bahia was impressed by the seedlessness and the rich flavor of this unusual orange." He sent twelve seedlings to the USDA in Washington, D.C., and the USDA propagated the trees and offered seedlings to anyone who wanted them. "In 1873, Mrs. Luther C. Tibbets, of Riverside, California, wrote for a pair of trees, got them and planted them in her yard. From them have descended virtually every navel orange grown on earth today." The ability to asexually propagate this sterile triploid has allowed the widespread dissemination of a single genotype with highly desirable characteristics.

One means of asexual propagation that is coming into widespread use in horticulture is the production of plants from cell or tissue culture. Meristem culture is used commercially to propagate a variety of plants such as orchids, begonias and Boston ferns. Plant cells are "totipotent," that is individual cells contain all the genetic information necessary to program the development and differentiation of the entire plant. In the 1970s it was shown that plant cells that had been grown in suspension culture would be plated out and induced to form embryo-like structures that developed into whole plants (reviewed by Torrey, 1985). This discovery opened the possibility of producing many thousands of genetically identical plants from the tissue of a single plant. Unfortunately, technical barriers to the regeneration of whole plants from single cells are still to be overcome for most economically important plants (*e.g.*, the cereal grains). Moreover, we have already seen that plant tissue cultures tend to be genetically unstable and exhibit high rates of chromosomal rearrangements.

Inbreeding and the creation of homozygous lines

Sex complicates matters! The processes of genetic segregation and recombination reassort combinations of genes in every generation. One way around this problem of ever-shifting combinations is to manipulate the mating structure and thereby control the genetic constitution of the progeny of specific matings. The first and most useful manipulation is enforced inbreeding. Inbreeding gradually eliminates heterozygosity and ultimately results in a collection of completely homozygous lines. Many plants can self-fertilize and under this most extreme form of inbreeding heterozygosity is reduced at the rate of one-half per generation. After ten generations of self-fertilization, heterozygosity is expected to be reduced by a factor of more than one thousand. Progeny of these homozygous lines will be virtually genetically identical to their parent, and as a result, a single desirable genotype can be propagated indefinitely.

One means of circumventing the years of inbreeding required to produce completely homozygous lines is the production of haploid plants. Haploid plants are sterile and the chromosome number must be doubled to restore fertility yielding a "doubled haploid" (DH) plant. Usually chromosome doubling is induced through colchicine treatment which interferes with the mitotic spindle apparatus. One means of producing haploid plants involves the use of anther culture. In barley, cultured anthers can be induced to form callus tissue and ultimately haploid plants (Choo *et al.*, 1985). These techniques show great promise, although some uncertainties remain. For example, in barley the success of haploid production seems to depend on genotype and not all plants recovered from anther culture are haploid (Choo *et al.*, 1985).

Many species of plants are predominantly self-pollinating in nature. The major grain crops of Old World agriculture (barley and wheat) are included in this category. Zohary (1984) notes that in contrast to wild plant species, most cultivated crop plants reproduced by either self-fertilization or vegetative propagation. It is significant in this regard that the wild relatives of wheat and barley also reproduce by self-fertilization. Presumably it was much easier for neolithic man to select and successfully propagate useful genotypes in plants where the selected lines bred true.

Crossing selected inbred lines and cytoplasmic male sterility

Maize is a predominantly outbreeding species. It is possible to self-fertilize maize plants, but the progeny of self-fertilized plants are much reduced in vigor and yielding ability. Moreover, maize exhibits the phenomenon of heterosis (highly heterozygous plants are superior in yield and other characteristics). There is an apparent conflict between the need to propagate high yielding genotypes and the requirement for highly heterozygous plants. The solution to this problem is to produce a large collection of highly inbred lines by self-fertilization; these lines are then intercrossed to produce highly heterozygous F_1 plants. The F_1s are then screened to select the best yielding hybrids. The selected hybrid genotype can then be propagated in large numbers by the intercrossing of its parental lines. A slightly more complicated procedure involves the intercrossing of selected F_1s to produce a double cross hybrid.

In many species the production of hybrids is difficult and involves the manual emasculation and pollination of individual plants. These tedious operations do not lend themselves to large-scale seed production. Fortunately, a genetically determined form of male sterility can often be used to circumvent this problem. A form of male sterility called cytoplasmic male sterility (CMS) occurs in many plant species and is widely used for the production of hybrid seed. At least three genetically distinct types of CMS have been characterized in maize (reviewed by Laughnan and Gabay-Laughnan, 1983). Recently, the mitochondrial genome has been implicated as the cytoplasmic locus of the CMS trait in maize (Sederhoff, 1984).

The main feature of CMS is the cytoplasmic transmission of male sterility, where expression of the male sterility trait is conditional on nuclear restorer genes. The restorer genes (denoted *Rf*) are usually dominant so that an *Rf*/*rf* heterozygote restores fertility in a male sterile cytoplasm. The important point is that cytoplasmic transmission is asymmetrical, because the extranuclear component is only transmitted through eggs (female lineages). This asymmetry can be manipulated to produce male fertile or male sterile progeny. For example, a cross of a CMS female to a pollen parent that is homozygous for the dominant restorer gene (*Rf*/*Rf*) yields fertile progeny. A cross to a homozygous recessive pollen parent (*rf*/*rf*) with a normal cytoplasm yields male sterile progeny. (This outcome follows because the female parent must be *rf*/*rf* to express the male sterile trait.)

The dependence of hybrid maize production on a particular CMS background called *cms*-T (Texas) provides a dramatic illustration of the vulnerability of crop systems based upon single genotypes. By 1970 more than 85% of the corn grown in the United States had the *cms*-T cytoplasm. The southern corn leaf blight epidemic decimated the corn crop because a fungal pathogen was specifically virulent on *cms*-T plants (Laughnan and Gabay-Laughnan, 1983). Substantial economic losses were sustained by U.S. agriculture due to the widespread utilization of a single genotype.

SELECTION AND TRANSFER OF PLANT GENES

Neolithic man did quite well as a plant breeder without any knowledge of the rules of genetic transmission. However, it would be a great mistake to infer from this success that genetics has little to contribute to crop improvement. Primitive man selected seed based upon the phenotype of the seed (maternal) parent without regard to the source of pollen genes. This selection scheme is called mass selection and is still a useful technique in improving cross pollinated crops. Nevertheless, our knowledge of transmission genetics allows the design of other more efficient selection schemes. In addition, primitive man had no *a priori* means of determining whether the phenotypic variation selected upon had a genetic basis. This consideration is particularly important for complicated traits influenced by many loci, such as seed yield in grain crops. Quantitative genetic theory provides methods for making these determinations and for the design of efficient selection schemes (where efficiency is defined in terms of progress per unit time).

The backcross method

A breeding method that has proved particularly useful in the transfer of traits determined by single genes is the backcross method. This method has been widely employed in the transfer of disease resistance genes from germplasm collections or from wild relatives into crop cultivars. The subject of genetic resistance to plant pathogens is fascinating because it involves the coevolution of the host plant and its pathogens. Genetic analysis of host plants often reveals that resistance is determined by one or a small number of genes (Ellingboe, 1981). The resistance genes are frequently race specific in the sense that a given gene only confers resistance against one or a few races of the pathogen. This relationship is known as the "gene-for-gene hypothesis." Genes that confer high levels of resistance are sometimes subject to severe infection from new pathogen races (which may be new mutants of the existing race). This complicated process of coevolution forces the plant breeder to be constantly vigilant for sources of disease resistance.

With this background we can now discuss the application of the backcross method to the transfer of a disease resistance gene from an unadapted germplasm source. We will use the term recurrent parent to refer to the recipient line. The first step is to cross the recurrent parent to the plant carrying the resistance gene. (We will call this plant the source parent and will assume that this plant is homozygous for resistance.) The progeny of this initial cross (F_1) will be heterozygous for all loci that differ between the two parents, including the disease resistance locus. If the source parent has agronomically undesirable characteristics, the genes determining these characteristics will also be transferred to the F_1 progeny. Next the F_1 is backcrossed to the recurrent parent (hence the name recurrent) and heterozygotes at the disease resistance locus are selected for the next generation. This step involves strong selection because approximately half of the progeny will be homozygous for the nonresistant gene. The selection step also requires that the heterozygotes be easily identified. This process of backcrossing and selection is then repeated a number of generations.

Our objective in performing repeated cycles of backcrossing and selection is twofold. First, we want to incorporate the disease resistance gene into the cultivar. Second, we want to eliminate all the other undesirable genes contributed by the source parent. The rate at which these other genes will be eliminated depends upon their linkage to the resistance locus. If r is the recombination fraction between the resistance locus and a second locus coding for an undesirable gene, then the undesirable gene will remain linked to the selected gene for an average of $1/r$ generations. For unlinked loci the average is two generations; for $r = 0.01$ the average is 100 generations. Clearly, 100 generations is too long for an economically feasible program. (Below we will consider the use of molecular markers as a way to speed up the process.) The time factor is one reason why the generation of useful mutants through mutagenesis of adapted cultivars is appealing. (We should note here that mutagenesis has been unsuccessful in producing new disease resistance genes.) Reducing the time factor is also one of the several advantages of the transfer of genes through molecular transformation.

Quantitative genetics

The backcross method focused on the transfer of a single gene. In many cases the desired phenotype will be controlled by many genes, each of small effect, so that

TABLE 2. *Elementary model of quantitative genetic transmission.*

Genotype	Frequency	Value	Frequency × value
G_1G_1	p^2	$+a$	p^2a
G_1G_2	$2pq$	d	$2pqd$
G_2G_2	q^2	$-a$	$-q^2a$

Population mean, $M = p^2a + 2pqd - q^2a = a(p - q) + 2dpq$

Variance, $V_g = p^2a^2 + 2pqd^2 + q^2a^2 - M^2$
$= 2pq(a + d(q - p)]^2 + (2pqd)^2$

the contribution of individual loci cannot be identified. In this situation, methods for analyzing the genetic basis of complex phenotypes must be developed. Quantitative genetics provides the methodological framework for this analysis by investigating the statistical relationship among relatives for important phenotypic characters (see Falconer, 1981, for an excellent elementary account of quantitative genetics theory).

To illustrate some of the basic features of quantitative genetics, let us consider grain yield in grams per plant. The first point to note is that this measure of phenotype is continuous, in contrast to the discrete phenotypic classes characteristic of disease resistance loci. Secondly, the distribution of grain yield per plant, taken over many plants, leads to a continuous distribution of variation. It is not possible to identify phenotypic differences with differences at individual genetic loci. Nevertheless, variation in grain yield is observed among plants and some of this variation may reflect genetic differences. Quantitative genetics provides a methodological framework for estimating the genetic contribution to this variation.

The first step in determining the genetic contribution to quantitative variation is to adopt a mathematical model of genetic transmission for quantitative characters. Initially we will focus on just one genetic locus that influences grain yield. Suppose there are two alleles at this locus (G_1 and G_2). We denote the relative frequencies of the G_1 and G_2 alleles in the population as p and q, respectively ($p + q = 1$). We will assume that we are going to perform mass selection on a random mating population. Table 2 presents the model where a and d denote the phenotypic values. The mean value of the trait taken over all three genotypes (hence the notation M) is also given in Table 2. Clearly, the mean will change as the frequencies of the genotypes in the population change.

An especially important concept is the average effect of substituting an allele at a genotype, averaged over the genotypes in which the allele occurs. We define $\alpha_1 = (pa + qd) - M$ as the average value of the G_1 allele and $\alpha_2 = (pd - qa) - M$ as the average value of G_2. Because genes and not genotypes are transmitted from parents to offspring, the average value of a gene is the central quantity in predicting phenotypic response to selection.

Table 2 also calculates the genetic variance (V_g). A second variance called the genic variance is calculated from the average values as $V_a = 2(p\alpha_1^2 + q\alpha_2^2)$. The subscript "a" denotes the fact that the genic variance (also called the additive variance) measures the fraction of the total variance that can be accounted for by the substitution of one allele for another. The difference, $V_g - V_a = V_d$, gives a third variance called the dominance variance which measures the nonadditive portion of the genetic variance. If many loci independently influence the phenotype (*e.g.*, grain yield) then the total variances taken over all loci are, $V_G = \Sigma V_g$, $V_A = \Sigma V_a$, and $V_D = \Sigma V_d$. If nonadditive effects operate between loci, then an interaction variance denoted V_I must also be specified. Thus, in general, $V_G = V_A + V_D + V_I$.

To continue our account of elementary quantitative genetics, we must adopt a general model of the relationship between genotype and phenotype. A linear model is assumed where phenotype = genotype + environmental influences + nonlinear interactions between genotype and environment. In symbolic terms $P = G + E + G \times E$. The $G \times E$ term is measured by replicating genotypes over a number of environments. It is usually desirable to produce cultivars that have stable yields over a range of environments, so a minimal $G \times E$ effect is sought. In some cases man can manipulate the environment to produce favorable genotype by environment interactions. One such case that has already been discussed is the use of dwarf mutants of rice in high fertilizer environments.

Let us neglect the G × E term and concentrate on the relationship among variance components. Applying the rules for calculating the variances of sums to the above equation we obtain $V_P = V_G + V_E + 2\mathrm{Cov}(G, E)$. Usually it is possible to ensure that $\mathrm{Cov}(G, E) = 0$ by replicating genotypes randomly over environments. This leaves us with $V_P = V_G + V_E$ which can be written in terms of the components of genetic variance deduced above as $V_P = V_E + V_A + V_D + V_I$. The final step is to estimate the four variances (V_A, V_D, V_I and V_E). The genetic components of variance are estimated from covariances among relatives. For example, it can be shown that the covariance among half-siblings is $\frac{1}{4}V_A + \frac{1}{16}V_I$ (neglecting small terms for interactions among three or more loci) and the parent-offspring covariance is $\frac{1}{2}V_A + \frac{1}{4}V_I$ (again, neglecting higher order interactions). In general, the components of variance are estimated by relating specific mating designs to the appropriate analysis of variance (Cockerham, 1963).

Once estimated, the components of variance can be used to calculate a statistic called the heritability and denoted $h^2 = V_A/V_P$. The heritability is the fraction of phenotypic variation that is due to additive genetic variance. This quantity measures the extent to which selection on parents will result in a change in the phenotypic mean of the offspring generation. The response to selection among the progeny can be shown to be $R = ih^2\sqrt{V_P}$, where i measures the intensity of selection (*i.e.*, the fraction of the parental population in the selected group). If h^2 is large (by definition h^2 takes on values between zero and one), mass selection should be quite effective in moving the population mean in the desired direction. Suppose $V_D > V_A$ so that there is considerable genetic variance, but h^2 is relatively small. In this case mass selection will not be very effective because parental phenotypes are not good predictors of progeny phenotypes. A progeny testing scheme, where parents are selected based on progeny performance, is better, although such a scheme entails more effort and a longer selection cycle.

There are many other extensions of quantitative genetics that aid in the choice of efficient strategies for plant improvement. These include analysis of the effects of selection on correlated characters, extensions to inbreeding populations, the construction of selection indices and selection on threshold characters.

The selection of interacting systems of genes

Complex phenotypes are determined by the integrated action of genes at several (or many) genetic loci. Some combinations of genes may interact favorably and it is clearly desirable to develop genetic strategies to select for favorable combinations. The key problem is to manage recombination and selection schemes in such a way as to maximize the chance for favorable combinations to arise. A variety of recurrent selection schemes have been proposed for this purpose (see *e.g.*, Allard, 1960). Recurrent selection schemes have the following general features. (1) A number of lines are selected from a foundation population and are individually inbred. (2) The inbred lines are tested for their performance and the high performing lines are selected for a second cycle. (3) The selected lines are interbred to produce a highly heterozygous population. (4) Step one above is repeated and the process of inbreeding, selection and intercrossing of selected lines is carried on for several cycles.

The intercrossing step is designed to allow recombination to bring favorable combinations of genes together and to retard the rate of inbreeding. Inbreeding by itself quickly leads to homozygosity and results in the random fixation of genes within a line. The rate of inbreeding must be retarded to enhance the opportunity for favorable combinations to appear. There are several methods used to test the performance of lines. One approach involves the selection of parents based upon the performance of test cross progeny. The parents may each be tested by crossing to a specific test cross line (specific combining ability) or they may be tested by mating to a series of tester lines (general combining ability). In either case the parents are selected for the next intercrossing cycle based on average progeny performance. A more elaborate scheme known as reciprocal recurrent selection is based on the parallel selection and intercrossing of two source populations, followed by the inbreeding of selected lines within populations.

Recurrent selection procedures have been important methods in plant improvement since the 1940s. The major limitation of these methods is the time consumed in carrying a population through a single cycle. Up to three generations are required to complete a cycle when progeny testing is employed. Time is always at a premium and methods of reducing the time invested in a breeding program have great appeal.

Selection in cell and tissue culture

The ability to plate out suspensions of plant cells and to regenerate individual plantlets in a few species of plants opens up the prospect of selecting for desirable phenotypes at the cell level, just as is routinely done in microbial genetics (Bliss, 1984). Traits that could be selected for in cell or tissue culture include resistance to toxins produced by pathogens, salt tolerance, tolerance to specific herbicides and heat or cold tolerance. The great appeal of these methods is the potential reduction in the time required to select for useful phenotypes and the modest demands on resources, as compared to conventional field experiments.

A number of obstacles still have to be overcome before the *in vitro* selection of plant cells achieves wide utility. These include difficulties in the regeneration of plants from cell culture for most economically important crop plants and the problems of genetic instability already discussed. In addition, the selection of complex quantitative traits will continue to be carried out at the whole plant level, at least until much more is known about the developmental and molecular genetics of complex phenotypes in plants.

Despite these obstacles, some applications of *in vitro* selection in plant cell and tissue culture have great promise. Torrey (1985) outlines the use of plant tissue culture methods to exploit the special biosynthetic pathways of plants. Plants produce a variety of useful secondary products including drugs, oils, pigments and fragrances. Tissue culture provides a means of producing these compounds and of selecting for useful modifications in their biosynthesis.

MOLECULAR APPROACHES TO PLANT IMPROVEMENT

Two factors constrain traditional plant breeding programs. The first factor is generation time. Rates of improvement per year are controlled by the generation time of the target plant species. We have already seen that recurrent selection schemes can consume up to three years per cycle, assuming one generation per year. Many important tree and fruit crops have much longer generation intervals, further limiting per year rates of progress. The second fundamental limitation is the reproductive confines of the target species. In the past, plant improvement has been restricted to the utilization of genetic variants that could be transferred to the target crop through sexual crosses. Molecular techniques provide a means to circumvent both of these limitations.

Use of restriction fragment length polymorphisms as genetic markers

One application of molecular technology that is applicable to virtually any crop species is the high density mapping of plant genomes using restriction fragment length polymorphisms (RFLPs). This technique represents a marriage of traditional genetics with molecular technology. The aim is to use a bank of randomly chosen DNA clones (either cDNA or genomic single copy clones) to search for restriction site polymorphisms. Cloned DNA fragments that are associated with polymorphic sites are then mapped using conventional test cross and F_2 progenies. This approach has been successfully applied to tomato where 41 unique cDNA clones have been mapped (Bernatzky and Tanksley, 1986).

There are several areas where high density linkage maps could be particularly useful in plant improvement. In our discussion of the backcross method we noted that a large number of backcross generations may be required for recombination to separate linked undesirable genes from the selected disease resistance locus. This time investment can be reduced if flanking genetic markers are available to monitor recombination events. When flanking markers are available large numbers of backcross progenies can be surveyed for recombinant events close to the locus of interest and these recombinant progeny can be selected for further propagation. This additional level of selection can achieve the same result at a savings of many backcross generations.

RFLPs and high density linkage maps can also be of substantial use in the genetic dissection of quantitative traits. When a few loci contribute to the bulk of the genetic variance for a quantitative trait, it may be possible to map these loci and to monitor their transfer by monitoring the transfer of their associated marker loci. The statistical basis for this use of markers was established over 25 years ago (see Mather and Jinks, 1971); however, adequate numbers of genetic markers have not been available in crop plant species.

There are two major advantages of RFLPs over conventional morphological markers. First, the number of RFLPs available is limited only by the number of single copy (or low copy number) clones that can be produced and this is certainly a large number. Second, RFLPs usually have no deleterious phenotypic effects, unlike most morphological markers. Consequently, the transfer of the marker into the cultivar under improvement has no undesirable phenotypic effects.

The transformation of novel genes into plant lineages

Genetic transformation has the potential of revolutionizing plant improvement. This technique can potentially overcome both of the major obstacles of time and reproductive barriers. With regard to the time obstacle, genetic transformation introduces individual DNA sequences, unlike sexual reproduction that transfers whole genomes. As a consequence, time consuming backcrossing programs become unnecessary when genes are transformed into plants. The real significance of genetic transformation, however, is that transformation allows the transfer of genetic material without regard to taxonomic barriers. In addition, it permits *in vitro* manipulation of DNA sequences such as the design of hybrid constructs from different genes, or the production of *in vitro* mutations at specific sites, prior to the transformation step.

At the current time, the most promising transformation system utilizes the Ti-plasmid of *Agrobacterium tumefaciens.* The Ti-plasmid is a large circular plasmid that has the property of introducing a portion of the plasmid (T-DNA) into plant genomes (Lawton and Chilton, 1984). Ordinarily, the T-DNA region contains oncogenes capable of inducing the tumorous growths associated with crown gall disease. The T-DNA also codes for opine production. This amino acid provides a novel carbon and nitrogen source for the growth of *A. tumefaciens.*

The important fact is that the T-DNA is capable of integrating into the plant genome for a wide range of plant species (a major exception appears to be the monocots). Thus the Ti-plasmid and its associated T-DNA represents an ideal system for the delivery and integration of foreign DNA into plant genomes. Engineered vectors have been constructed where the oncogenic regions of the T-DNA are deleted and where drug resistance genes have been inserted as selectable markers. In addition, the regulatory regions of the genes involved in opine synthesis can be inserted in front of the foreign gene (the gene that is to be transformed into the plant), to control expression of the foreign gene when the T-DNA is integrated. The actual transformation involves the introduction of the engineered Ti-plasmid into plant cells in cell culture (this currently limits Ti-transformation to plants that can be regenerated from individual cells). These techniques have been used to introduce the yeast alcohol dehydrogenase gene into tobacco and the maize zein gene into sunflower.

Much of the current commercial activity in plant genetic engineering is centered around the production of plants resistant to specific herbicides. These alterations would permit large chemical companies to tailor plants to specific herbicides which would presumably enhance the potential market for the herbicide. In addition, many serious weeds have evolved resistance to common herbicides while crop plants remain susceptible. It would clearly be desirable to introduce resistance genes into crop plants that are absent in associated weed populations.

A recent example of commercial efforts to engineer plants resistant to the herbicide glyphosate is described in the October 1985 issue of *Genetic Engineering News* (p. 16). This herbicide blocks the synthesis of aromatic amino acids. A gene for low sensitivity to glyphosate has been identified in the bacterium *Salmonella murium.* This bacterial gene has been transformed into tobacco cells using a Ti-plasmid derived vector and tobacco plants with some resistance to glyphosate have been regenerated.

To illustrate how complex genetic engineering manipulations can become, we will end with a brief consideration of the gene that codes for a component of electron transport in the chloroplast genome. The gene (denoted psbA) codes for a polypeptide called the "32 kilodalton" thylakoid membrane protein. Triazine herbicides bind to this polypeptide and thereby block electron transport, depriving the plant of energy from photosynthesis. Natural mutants of psbA occur in some weed populations that are resistant to triazines. In *Amaranthus hybridus* the gene for the resistant form has been cloned, sequenced and shown to differ from the susceptible form by a single amino acid substitution (Hirschberg and McIntosh, 1983).

It may be possible to insert a resistant copy of the psbA gene into the chloroplast genome through Ti-plasmid transformation; however, there are some obstacles. One obstacle is the fact that the chloroplast genome is present in many copies in each cell. An alternate strategy is to transform the resistant psbA gene into the nuclear genome and then have the resulting polypeptide transported into the chloroplast. To achieve expression of a chloroplast-encoded gene in the nuclear genome, appropriate promoter sequences must be added to the psbA coding sequence for transcription by the nuclear polymerases. The transport problem can also be solved by using transit peptides from other nuclear-encoded genes that are chloroplast components. The sequences coding for the transit peptide of the small subunit of ribulose-1,5-bisphosphate carboxylase can be ligated to the 5′ end of the psbA coding sequence for this purpose. Informal reports suggest that preliminary experiments of this kind have been successful (*Science*, 6 December 1985, pp. 1148–1150).

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Science as a Way of Knowing: Human Genetics[1]

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SYNOPSIS. Genetics contributes to our way of knowing in two ways: 1) there is an analytical method that sorts out relationships between genes and phenotypes and 2) the genes transmit biological information, specify cellular structure, and mediate homeostasis and development. Human genetics can be used to clarify many aspects of human variation. The paper deals with three: 1) the meaning of individuality; 2) the nature of causes; and 3) possibilities and limits for goals in medicine.

The genes define individuals as unique representatives of many classes. They contribute variability to the qualities of each class. Phenotypes have two kinds of causes (Mayr, 1983): proximate causes lead to events consequent upon decoding of the DNA, while ultimate causes consist of the genetic and cultural events that shape the species and the individuals of which they are composed. Disease is a consequence of incongruence between a genetically conditioned homeostasis and experiences and events. The genes set limits for homeostatic response thereby limiting both the forms and expressions disease can take in various individuals and the extent to which the latter can be modified by treatments of various kinds.

Science as a way of knowing is a phrase with a degree of ambiguity. First, it suggests that science is a pathway to a desirable goal, perhaps that of knowing oneself, or of understanding electricity. But then, science is also a design for knowing, a matrix to give conherence to the strands of experience, one of the looms on which the fabric of knowledge is woven.

Genetics exemplifies both of these "ways." Its analytical method is a means to an end; it accounts for the variation observed in populations, traces the origins of phenotypes to genes, differentiates individuals, families and populations, and ferrets out homogeneous components from heterogeneous samples. It introduces order. And as for a design for knowing, the genes are the architects of biological structure, the mediators of development and homeostasis and the keepers and transmitters of biological information. It is clearly not possible to comprehend biology in any but a genetic context.

Human biology has not, until recently, had much of a genetic tradition, probably because human biology has focussed mainly on disease in which immediate causes, pathogenesis and treatment are paramount. But now technological advances have stimulated a keen interest in the genetic origins of human differences of all kinds.

There is little to distinguish human genetics from any other; the mechanisms are the same in principle, if not always in detail. So the question to be examined here is what are the uses to which we put our knowledge of human variation? How does genetics help us to know ourselves?

I would like to examine three ways. A knowledge of genetics is essential for a good grasp of a) the meaning of individuality, b) the nature of causes, and c) possibilities and limits for goals in medicine.

INDIVIDUALITY

Two kinds of individuality

As every biologist knows we express our individuality in two ways. First, we are each representative of numerous classes; for example, sex, religion, and national group, and we are also poker players, diabetics, or members of the American Society of Zoologists. In each class the individuals are distinguished only by the characteristics of the class. On the other hand, each of us is in a class of our own, representative only of ourselves by virtue of the uniqueness of our endowment and experiences. Genetics gives us some insights into both of these kinds of individuality and helps to resolve controversies that arise out of confusing them. For example, when comparisons between groups reveal differences, there is a tendency to label the groups typologically, when, in fact, the differences within the groups may exceed those between. This is what Ernst Mayr (1961, 1983) calls typological thinking or essentialism. Its antithesis is population thinking. The latter takes into account the individuality expressed in populations and describes differences between them as a consequence of overlapping distributions rather than of typological distinctions. It was just such typological thinking that characterized the muddle that swirled around the supposed association of the XYY karyotype with antisocial behavior. Since the first cases were discovered in prisons, it was presumed in some quarters that men with an extra Y chromosome were doomed to a life of crime. The press even called the Y the "violence" chromosome, in plain disregard for the pacific character of most of its possessors. Later, population studies revealed that those with two Ys were somewhat more at risk for behavioral aberration than those with one; the former were about as variable as the latter (Witkin *et al.*, 1977).

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[1] From the Symposium on *Science as a Way of Knowing—Genetics* presented at the Annual Meeting of the American Society of Zoologists, 27–30 December 1985, at Baltimore, Maryland.

Polymorphism

What is the extent of the genetic variation on which human individuality is based? Until 25–30 years ago it was generally assumed that human genotypes were largely homozygous; the relatively few mutants were assumed to be bad and to constitute a genetic "load" (Muller, 1950). Now we know that human beings are genetically highly polymorphic; that is, there are constellations of alleles for many gene loci in which two or more exist in frequencies of more than one percent (Harris, 1980). Electrophoretic differences in soluble enzymes, plasma constituents and other proteins suggest individual heterozygosity at 1–6% of loci, and since electrophoresis fails to discover all variants, this may be a considerable underestimate (McConkey *et al.*, 1979; Harris, 1980; Rosenblum *et al.*, 1983). And, of course, each of us has some rare familial variants and some new ones. Recombinant DNA methods have shown even more extensive polymorphism in introns and flanking regions, and these have proved useful as markers in mapping the chromosomes as well as in antenatal diagnosis (White, 1984). Surely all this variation, compounded by experiences, is more than enough to account for the immense range of apparent individuality which, as I shall point out later, has its counterpart in the various ways people get sick.

Most polymorphisms are found in all populations regardless of race; for example, the loci of the major histocompatibility complex have been found everywhere to be so variable as to cause nearly everyone to be heterozygous for each; but a few polymorphisms are geographically circumscribed; hemoglobin S in Mediterranean people and alpha-thalassemia in the Far East are examples.

We are accustomed to thinking about genes and their effects one by one, and as inherited independently. But, in making it possible to study chromosome structure, even to observe the details of DNA strands that sometimes include several loci transmitted together, modern techniques are giving us glimpses of new dimensions of individuality. For example, by examining the allelic composition, or haplotypes, of the several MHC loci, together with neighboring loci that specify elements of the complement cascade, it is possible to relate clinical differences in patients with immunological disorders to particular concatenations of genes (Ryder *et al.*, 1981; Alper *et al.*, 1982) (Table 1). Some of these allelic combinations are observed more often than chance would allow; they are in linkage disequilibrium (Bodmer and Bodmer, 1978). Presumably together they exert a stronger or different effect than that possible for each alone, thereby substantiating the axiom that selection acts not on genes but on phenotypes. Other interacting (or modifying) genes may exist at unrelated loci. Their discovery is likely to be among the benefits of chromosome mapping which should lead to the assembly of lists of genes accounting for variation within particular

TABLE 1. *Haplotypes associated with disease.*

Haplotype	Association
A3, BW47, DR7, BFF, C2C, C4AQO	21 OH'ase deficiency
AW30, B18, DR3, BFF1	Diabetes (IDD)
A1, B8, DR3	Several diseases

From Alper *et al.*, 1982.

phenotypes. And, of course, individuality is also strongly conditioned by development, experiences, the environment and particularly by learning. The latter has heritable features also, some of which resemble genetic inheritance (Cavalli-Sforza *et al.*, 1981, 1982).

These relationship of genes and experiences to individuality and to the distribution of phenotypes in populations represents population thinking. It is a way of knowing, and human affairs, both biological and social, are incomprehensible in any other setting. Essentialism, in contrast, in giving primacy to stereotypes, to the general rather than the particular, in embracing many under a rubric that describes only some, however useful or even necessary in classification and economical disposition of diverse classes, risks lending plausibility to ideology.

CAUSES

Ernst Mayr (1961, 1983) has pointed out that, until this century, biology was divided between medicine (including physiology) and natural history. Medicine and physiology, he goes on to say, deal with function; they are concerned with questions of how—how things are put together and how they work, and, we might add, how they go awry. The answers to these questions about function will reveal what Mayr calls proximate causes, which lead to everything that happens after the decoding of the genetic program. In contrast, students of natural history ask questions about why; of how things came to be what they are. These are questions about ultimate causes, about evolution; they are questions about the history of genetic programs, and of how they take shape and change. The mechanisms involved in the evolution of species give form and substance to individuals who become the testing grounds for new versions and new combinations of old genes. Obviously, no biological question can be said to be fully understood until both kinds of question have been answered. Human genetics contributes to our understanding of both kinds of cause.

Proximate causes will be elaborated more fully in the section devoted to medicine. Here I consider ultimate causes.

Effects of ultimate causes

If proximate causes of individuality are the outcomes of specific genetic programs, ultimate causes determine what kinds of programs are possible. They constrain, they set the limits to the forms the genotype is capable of specifying. Such constraints are expressed in the complex homeostatic systems required to maintain a steady state in the varied environments human beings encounter. It is our evolutionary history that makes us human, a history that is written in the nucleotide sequences of the DNA and in the amino acid sequences of the proteins. Such sequences show how the human genome evolved; for example the origins of the several globin loci are readily visualized in both DNA and amino acid sequences of the human and other hemoglobins (Orkin and Kazazian, 1984). A spectacular demonstration of the evolution of several families of genes engaged in immunological missions, written in DNA sequences has been provided by Hood and his colleagues (Hood *et al.*, 1985). And observations of DNA and amino acid arrangements of the proteins of organisms ranging from microorganisms to man not only validate phylogenetic trees based on morphological evidence, but show that changes occur with a regularity that suggests an evolutionary clock (Wilson, 1985). The inescapable conclusion is that we human beings, for all our intellectual power and technological prowess, are caught up in a biological network from which we shall not easily escape, despite all our boasts that we now control our own evolution.

MEDICINE

If genetics provides a way of knowing individuality, it should be central to the study of medicine and yet it is given a subsidiary place in the medical curriculum, if any at all (Childs *et al.*, 1981). It is true that all teaching hospitals have medical genetics clinics for the care of patients with "genetic" diseases, including inborn errors, chromosome abnormalities and anomalies of development. But this is evidence that genetic disease has been classified typologically. Other kinds of disease classified as, say, endocrine, immunological, pulmonary or renal, even though plainly influenced by the genes, are not attended by medical geneticists, and there is a significant risk that their familial aspects will be ignored. Why should this be?

Limitations of the past

A minor reason is that genetics has no tradition in medical education and practice. Unlike biochemistry, physiology, and molecular biology which flourished in medical schools from the start, genetics was introduced more often than not by zoologists and botanists who, because they knew Mendelian genetics, were able to counsel families about reproductive risks.

A more compelling reason is that medical people just do not think genetically; medicine is still largely essentialist; population thinking has yet to achieve any widespread appeal (Childs, 1982). Perhaps this is not surprising, is even to be expected. The last 20 or 30 years are characterized by an immense expansion of knowledge of biological structure and function. Biochemists and molecular biologists have been elaborating the fundamental rules of homeostasis as they apply to (among many organisms) *Homo sapiens,* while medical investigators have been applying the newly acquired information to the elucidation of the pathogenesis of disease. Both groups focus piercingly but narrowly on proximate causes. In all this, variability would be a nuisance. So, individuality has been shunted aside in the interest of working out prototypes. But, unfortunately, prototypic teaching does not cultivate curiosity about the variability that inevitably modifies the prototype. Neither does it arouse much curiosity about the origins of variability nor about its limits or the constraints those limits put on types of disease and their signs, symptoms and susceptibility to treatment. It overlooks ultimate causes.

A third reason is the exigence of disease. It is the effects of proximate causes that are treatable; for example, ultimate causes are peripheral to events in a coronary care unit. It is the *fact* of a disease, its symptoms of discomfort and disability, its signs of homeostatic stress, its mere existence, that pose the problems with which investigators struggle. So the ways medical information is generated and the ways the conventional missions of medicine are pursued conspire against an emphasis on variability, and rather than liberating medical thought, genetics has been subordinated to serve a traditional and typological role in the classification of disease and the organization of medical care.

Signs of Change

Genetic heterogeneity

But, as everyone knows, there are signs of change. For years, human geneticists have been pursuing the Holy Grail of heterogeneity, one of the many aliases behind which individuality hides. Heterogeneity simply means the manifold genetic origins of like phenotypes, and it can underlie differences in age at onset, severity, clinical expression, even mode of inheritance of disease or other phenotypes. This quest has been much advanced by the advent of recombinant DNA methods. Observation of base sequences has turned up many kinds of mutations in human DNA (Table 2). All of those listed have been observed in hemoglobin variants, most in beta thalassemia. And for each type of mutation there are numerous possible variations, many already described, others awaiting discovery. Obviously, the elucidation of heterogeneity has implications not only for the dissection of the human genome and the measure of its range of variation, but also for the design of treatments specific for genetic cause. Now the whole of the human genome is a hunting ground for the detection of restriction fragment length polymorphisms, deletions and other quarry

(White, 1984). For example, at a meeting last summer it was reported that over 800 genes have been mapped, while regionally localized DNA segments not known to represent specific genes, but of use in mapping, number in excess of 500. The X-chromosome is the best known, with 214 mapped sites (Chapelle, 1985). All of these numbers are immediately overtaken by events and the tempo of discovery is such as to suggest that the means are at hand to define the whole map. Further, since genes can be discovered in the absence of knowledge of their product or its role in homeostasis, it may become possible to practice a kind of upside-down genetics in which phenotypes are traced from the gene, rather than the other way around. An important outcome of this mapping of genes will be the characterization and enumeration of the molecular variability of cellular structure and homeostatic mechanisms; the pathways, cascades, mosaics and networks of interlocking and communicating systems. In turn, these details will be used in explaining the processes of disease and the design of new treatments. And in bringing together mechanism and individual variation, genetics is likely to move into the mainstream of medical thought and practice, by going beyond inborn errors, anomalies and chromosome aberrations to define the genetic contributions to the common diseases of adult life. The former are numerous, rare, burdensome, resistant to treatment and largely confined to prepubertal life. The latter, mainly representing postpubertal disease, are less numerous, more frequent, less burdensome as to mortality, and more likely to respond to ameliorative treatment. They are believed to be multifactorial in origin; genetic susceptibility is suggested by familial aggregation of cases and partial concordance of monozygotic twins; and special provocative and precipitating experiences are postulated.

A continuum of disease

This is a typological description of what appear to be two kinds of disorder. But the differences may be largely illusory. If disease is defined as incongruence between homeostasis and experience, then it can be shown that there is a continuum of disease to which the genetic contribution declines from conception to old age. First, intrauterine selection is intense; up to three-fourths of conceptuses do not make it to term and the evidence suggests that many of the losses are genetic (Roberts and Lowe, 1975; Edmonds *et al.*, 1982). Second, much of the mortality of the first year of life is also genetic, and in general, onsets of monogenic diseases decline rapidly with age; more than 90% of such disorders have declared themselves by puberty, only about 1% after 40 (Costa *et al.*, 1985). Third, in postpubertal diseases the cases of early onset are more likely than those of later onset to be severe, more life-threatening, more resistant to treatment, and more likely to to have affected relatives (Childs and Scriver, 1986). That the latter represents concentrations of genes in the cases of early onset is suggested by the aggregation in the younger cases of several autoimmune diseases of certain immunologically significant polymorphic alleles (Childs and Scriver, 1986). And fourth, advancing age is accompanied by a narrowing list of diseases; people with genes predisposing to disease are likely to come down with them before old age (Kohn, 1982). Taken altogether this evidence suggests a gradient of genetic effect that wanes throughout life. The most selectively disadaptive genes exert their effects with minimal reference to the rest of the genotype or the environment, and they tend to do so early in life.

TABLE 2. *Kinds of mutation found in human DNA.*

- Missense
- Deletions
- Nonfunctional mRNA
  - Nonsense mutations
  - Frameshifts
- RNA processing mutants
  - Splice junction
  - Consensus changes
  - Occult sites
- Promoter region mutants
- RNA cleavage mutants
- Position effect mutants

After Kazazian, 1985.

Others specify a Mendelian phenotype, but one that is modifiable by other genes and by experiences. Still others merely predispose to disease; they are disadaptive only in the presence of certain other genes and of special circumstances and experiences, and they are likely to have onset in adult life. So there are monogenic disorders and multifactorial disorders and some diseases have versions of both; diabetes and gout are examples (Childs and Scriver, 1986). Some cases, usually of early onset and often the most severe, segregate as Mendelian phenotypes, while others, usually of later onset and of milder expression, are irregularly familial, suggesting multifactorial origin. And those of latest onset, the least affected by genetic variation, are most obviously associated with special experiences. That is, monogenic and multifactorial disorders are not typologically distinct either in expression or cause, but differ only in the degree of selective disadvantage imparted by the genes involved. The typological distinction is based on the artifact of Mendelian segregation of the monogenic phenotypes—I say artifact because the genes of the multifactorial conditions are no less Mendelizing; it is just that their effects are individually less salient. The typological distinction is also less than compelling when we consider ultimate causes. The genes that promote disease are a product of the processes that engender the variation necessary for evolution. Those processes are indifferent to outcome; mutation, recombination and segregation of chromosomes merely generate the variation that is tested in living. Most is the stuff whereby the species prospers, but some is incompatible with any life, some is disadaptive when in conjunction with special experiences. That which is incompatible with life is most likely to be a consequence of mutation at one locus or a major chromosomal aberration; individual susceptibility is more likely to be associated with several or many genes. But only likely; we know of single gene differences and chromosomal aberrations compatible with good health and there are multigenic developmental disasters. So we do best to see disease as a continuum with emphasis on disadaptive genes in early life and adverse experiences later on. A cohort of human beings is at its most variable genetically at conception and at its least in old age. Conversely, variability due to experience increases with age.

Management of disease

Is this simply an interesting observation or can it help in practical ways in our struggle with disease? It may help most in emphasizing the genetic contribution to susceptibility to disease and in defining limits to success in treatment and prevention.

Presumably gene mapping will proceed until we know most of the disadaptive genes that cause the monogenic disorders, as well as the special combinations most frequently associated with the more common multifactorial diseases. These observations should be helpful in the discovery of proximate causes, and in defining the three elements that are required for the design of treatment and prevention. They are: a) the gene products and the part they play in homeostatic systems; b) the experiences that stress such systems; and c) the consequences of such incompatibilities, that is, pathogenesis. When all are known, we may be able to envision how to nullify some critical step in pathogenesis, or to minimize or eliminate the environmental stressor.

Treatment

Treatment is most successful when the precipitating factors and pathogenesis are known and all genotypes are equally susceptible (Table 3). In such cases—infections and nutritional diseases are examples—an actual cure is effected by removing the offending agent or by supplying the deficiency. It is next best when something is known of both provoking experiences and pathogenesis, and when individual susceptibility is observed to be a product of several genes. Some of these diseases, although incurable, are kept in abeyance by environmental manipulation. For example, insulin-dependent diabetes is treated with insulin and non-insulin dependent diabetes is controlled by diet and weight loss. Treatments are sometimes moderately successful in monogenic disorders when the provocation is known,

TABLE 3. *Success of treatment and prevention depending upon knowledge of genes, provocations and pathogenesis.*

Genes	Experiences	Pathogenesis	Treatment	Prevention
1. None	Known	Known	+++	++++
2. Multiple	Known	Known	++	+++
3. Multiple	Unknown	Known	++	– –
4. Mono	Known	Known	++	±
5. Mono	Unknown	Known	+	– –
6. Mono	None	Known	– –	– –
7. Mono	None	Unknown	– –	– –

although often lifelong and sometimes difficult to maintain. Phenylketonuria, galactosemia, and the adrenogenital syndrome are examples of such success. Treatment is least successful in monogenic disorders in which the gene effect prevails over all environments, regardless of whether or not the details of pathogenesis are known. None of these monogenic disorders can be said to be cured.

Here we are seeing the effects of ultimate causes; that is there is an inverse relationship between success in treatment and the intensity of selection against the gene effects. The more profound the transgression of adaptation, the less likely is even a plausible treatment to work. Where there is no experience or condition of the environment that contributes to the cause, our interventions are usually unavailing; except perhaps where the disadaptive effect is pretty mild anyway, or occasionally, when there is a definitive surgical solution (Hayes *et al.*, 1985).

Prevention

Prevention is most successful when the precipitating experiences are known and can be manipulated (Table 3). And because pathogenic changes are likely to leave some scars, however inapparent, prevention is likely to be more in the patient's interest than any treatment, even though the latter may represent a cure. As with treatment there is a progression of lessening success with increase in the disadaptive qualities of the genes. The position is least ambiguous when the provocation acts equally over all genotypes. Such disorders—lead intoxication and nutritional diseases are examples—might be called diseases of society rather than of individuals, since they occur most frequently among those denied the benefits of social organization. The greatest ambiguity is met in monogenic disorders expressed only in the presence of a precipitant. When the latter is a dietary necessity such as milk, even when the manifestations can be controlled by appropriate adjustment as in phenylketonuria and galactosemia, the disease cannot be said to have been prevented. But when the provocation is a drug, as in glucose 6-phosphate dehydrogenase deficiency, the expression can be prevented altogether by withholding it.

Antenatal diagnosis

So here again are seen the subtle constraints of ultimate causes. Prevention is no more successful than treatment when the mutant exerts its effects over all environments. But if those constraints will not be denied, one way out is to anticipate them. When a diagnosis of an untreatable disease can be made early in gestation it is possible, paradoxically, to prevent the disease by preventing the birth of affected fetuses. This is a definitive, and for many physicians and families acceptable, solution for severe disease, and it is now possible to make an antenatal diagnosis of more than 150 such disorders (Epstein *et al.*, 1983). Here again the limits are set entirely by the techniques available and the energy with which they are applied. Uncertainty enters in when the disorder is more or less treatable or has a delayed onset. And, of course, the method is useful, except in a limited number of cases, only in families concerned about recurrence; widespread discovery of heterozygotes is not yet possible. But it is a solution of wide appeal and one that is in tune with nature; most diseases for which the method is appropriate are under heavy adverse selection. And it is one that will be greatly expanded as a result of the "new genetics."

The future

We are all wondering just now what other impacts the "new genetics" will have on diagnosis, treatment, and prevention. Will it transform medicine and, together with other technological advances, lead to a society free of disease in which human beings, after serene untroubled lives, die of programmed senescence at around 85? The idea can be dismissed as nonbiological; it denies the constraints of ultimate causes. At a minimum, even if all precipitating provocative experiences were known and could be nullified, there would remain those genes that exert their bad effects without any such provocations. But since man is adapted to the conditions of the past, not the future, and since the creation of new environments and experiences uniquely characterizes human beings, no environment non-threatening to a genetically diverse population is likely ever to prevail, even if society wished it, which it most manifestly does not. So the question is not the recreation of the garden of Eden, but of *how much* we can reduce the nongenetic contribution to disease.

Genes and susceptibility

Gene mapping promises to be helpful in discovering markers associated with disease. Here, immediate utility will be directly proportional to the strength of the adverse selection. When a single mutant can be exposed as a cause there is hope for some kind of definitive disposition because of the reciprocal relationship between success in treatment and the appositeness of antenatal diagnosis and abortion; for genes of strongly adverse effect the latter may be preferred, for milder cases the former.

But ambiguity will increase as the map density increases. Some genes will be shown to be strongly associated with disease and may be inferred to be a part of cause, and as such they will be useful in unravelling pathogenesis. But not all will carry equal weight. For example, if alleles representative of several loci are found in a majority of the cases of a disease, we will wish to explore which loci furnish the genes most directly related to the pathogenesis. Perhaps two or three will be seen to supply the main culprits with others as modifiers, perhaps to heighten severity or make for earlier onset. Other genes, shown to be merely linked to those implicated in cause, may have use as markers, or as indicators for further exploration in search of genes involved in cause.

But most of these genes are likely to have limited utility as diagnostic indicators. Since most multifactorial diseases are common, the genes are likely to be polymorphic, so many more people will have them without disease than with. Even so, relative risks can be calculated and occasionally the genes may have some utility as evidences of susceptibility. Some, like the now celebrated low density lipoprotein receptor mutants, may represent a risk of such moment as to require drugs or special diets (Goldstein and Brown, 1985), others may be a mixed blessing. That is, although the relative risk may be, say, 5–10-fold, the probability of getting the disease may still be low. Further, relative risks are based on populations and so are not equally applicable to each member thereof. So, the knowledge that one has one or more genes commonly associated with particular diseases may represent data of uncertain meaning but which may carry a potential psychological impact grossly out of proportion to the biological risk. There is also the fear of early discovery in individuals of genes that produce disabling and untreatable diseases with onsets in middle life, again with a psychological impact, this time perhaps not so disproportionate (Wexler, 1985). So, these genes will have uses in understanding the nature and variability of diseases, but we may have to wait for a more thorough knowledge of their functional significance, singly and in combination and in relation to specific experiences, before we can use them wisely in diagnosis or prevention.

Gene therapy

There are other applications of the new genetics known in medicine as gene therapy. Given the less than spectacular record of treatment of monogenic diseases, it is no surprise that investigators should wish to substitute good genes for bad (Friedmann, 1983). It is intellectually strongly appealing since in theory it overcomes the evolutionary constraints that inhibit conventional treatment. It circumvents homeostasis altogether, simply correcting the defect in the gene that is reflected in homeostatic breakdown. Such gene substitutions have been accomplished in animals so plans are afoot to try it in human beings, perhaps to begin by transforming cells of the bone marrow in cases of an invariably fatal immunodeficiency. After surmounting inevitable problems it may well succeed and other conditions will be tried. But for all the hundreds of monogenic diseases listed in McKusick's catalogue or for the thousands yet undescribed, quite apart from the numerous technological problems yet to be faced, or perhaps yet even to be imagined, no one can predict the outcome. Perhaps the constraints, so easily thrust aside in theory, may in practice limit the number of conditions tractable to gene therapy. Or it may turn out that the ultimate constraint will be financial.

CONCLUSION

In conclusion, genetics helps us to know ourselves, both as a species and as individuals, and to know how we came to be what we are. It also shows us that some disease is an inevitable by-product of the mechanisms for supplying the variability essential for a successful species. Curiously, it has not had much impact on medical thinking, but it is likely that the methods of the new genetics will remedy that deficiency by establishing the idea of genetic variation as essential to the study of human biology and medicine.

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Cultural Evolution[1]

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SYNOPSIS. Culture is made possible by the existence of mechanisms of learning and communication. Because of it, we can profit from the experience and ideas of others. It is convenient to include in it tools, technologies, and all culturally transmitted behaviors. At least from an evolutionary point of view, they share common mechanisms. It is also becoming increasingly clear that animals share with us potential for cultural adaptation, which is however much more highly developed in humans, as shown for instance, by the extension of human brain areas that are involved in control of hand and phonation organs.

To understand how culture evolves one can make resort to models that map reasonably well after the necessary substitutions, into those that have been useful in biology. A major difference that one finds is in mechanisms of transmission, which are much more varied in culture than in biology. Parent-child (vertical) transmission is present in both. An "infectious" (horizontal) mechanism is characteristic of cultural transmission, but is practically absent in the genetic case. Other mechanisms of transmission are reviewed, along with their evolutionary consequences. The variety of these mechanisms can make culture extremely fast and flexible, and there are the great advantages of cultural adaptation *vs.* genetic adaptation by natural selection, or *vs.* physiological adaptations (which are relatively fast but highly specific: for instance, tanning under exposure to UV). But culture can also be extremely conservative. Also, some cultural transmission mechanisms allow heterogeneity between individuals to persist, others tend to make populations extremely homogeneous.

The study of culture from an evolutionary point of view is young, but very promising.

Living beings show remarkable adaptations to an enormous variety of environments. Such adaptations have usually been reached by the preferential reproduction of forms that were better endowed with the capacity to survive in certain environments and to multiply, and the properties which made them more successful were passed to progeny. This is adaptation by natural selection; it is reached slowly. Certain mechanisms have been developed which allow faster adaptations. Among them, one requires the capacity of learning from the experience of others. It seems to me that this is the very essence of what I like to call culture, and it requires some form of communication. Learning can take place by simple imitation of the behavior of other individuals, in which case communication is restricted to visual or similar cues. There are however situations in which some type of teaching takes place, so that the individual capable of a specific action or skill takes the initiative of transmitting this behavior or skill to other individuals.

DEFINITION OF CULTURE

There is some danger in trying to define culture. Cultural anthropologists have tried and largely failed as demonstrated by the enormous number of definitions that have been suggested in the literature (over 150 before 1960). Fortunately we can escape this problem by noting that the most common layman's definition of culture is perfectly adequate. If we look up this word in Webster's dictionary in fact, as well as in other dictionaries, we find that the two ideas of learning and transmission are essential to a definition of culture. It is fortunate that Webster's definition includes both the ability of making tools and any learned behavior relevant to our social or intellectual lives or endeavors. Tools seem to be an important part of culture, which is certainly learned and transmitted. Our main interest is the evolution of culture, and it will be useful to collect together all cultural phenomena which have something in common from an evolutionary point of view. From this vantage point it is convenient to give culture as general a definition as possible at the outset, and consider if different cultural phenomena are affected by similar evolutionary mechanisms.

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[1] From the Symposium on *Science as a Way of Knowing—Genetics* presented at the Annual Meeting of the American Society of Zoologists, 27–30 December 1985, at Baltimore, Maryland.

CULTURE IN ANIMALS

Speaking of culture, the mind of the student goes immediately to humans. It is true, in fact, that the human species is the one which has developed to the greatest extent as far as we know today mechanisms that we call cultural adaptation. It would, however, be a serious mistake to conclude that animals do not have culture. They not only do, but they probably have much more of it than we realize today. The subject has become of interest only fairly recently, but there already are in the literature a number of observations that show how cultural transmission and evolution are important also in animals. One recent example of tool use has obtained very widespread attention: the particular behavior of chimps which goes under the name of termiting (McGrew *et al.*, 1979). Chimpanzees are very fond of termites. They obtain them by using little sticks to pry open the tunnels in which termites shelter themselves from light. This is however far from being the only example, and it is not only chimps that show an interest in developing new tools. Beck (1980) lists a great number of examples of animal tool behavior which have been known for some time.

Apart from proper tool use, there are many examples that might not perhaps be described as tool use under some definitions, in which there is a learned behavior certainly passed on from generation to generation (almost always from parent to child, but sometimes also between individuals of the same generation). One example of learned behavior, among very many, that is passed from parents is that of the oyster catcher. Here it is interesting to remember that at least two ways of opening oysters are employed. One is by hammering the oyster with the beak until the shell is broken. Another is to attack the oyster under the water while the valves are open, introduce the beak and use it as a knife to cut the muscle that closes the valves. It has been shown that by replacing eggs of one variety into the nest of the other variety oyster catchers can learn one or the other technique.

This and other examples of learning and transmission by animals are listed by Bonner (1980) who provides a summary of some of the existing information that is most satisfactory for class teaching. A classical example is that of the blue tit, which in the years following World War II learned to feed on cream by opening the tin foil caps of milk bottles. This innovation spread very rapidly to the other birds and after a relatively short time it was necessary for milk distributors in England to replace tin caps with caps resistant to blue tits, in order to be able to continue the custom of leaving bottles unattended outside doors in the morning.

Perhaps the most elaborate study of the origin and diffusion of innovations in an animal colony is one among Japanese macaques which took place in a small island near Japan. These macaques learned a variety of new things, among them swimming, and they now enjoy spending a considerable part of the time in water. Their confidence with water has increased to a point that one Japanese macaque swam to a new neighboring island. Swimming was certainly not the only innovation. There were at least two, which were responses to initiatives by the scientists studying the colony. The first of these was the washing of potatoes in the sea water. The stimulus to this innovation was that investigators left potatoes on the sand near the sea. Washing had the advantage of easily removing the sand. The inventor was a female macaque whose name was Imo, a genius of the species. Her second known invention was the flotation of cereal seeds which had been left on the sand. Seeds were thrown by the macaques into the sea, where they floated letting the sand sink to the bottom. This is similar to a technique used by man for the extraction of minerals. It is of interest that only females or younger individuals accepted the innovation and others, especially old males, never showed any sign of interest. Females then transmitted the innovation to their children.

There is now a growing body of evidence

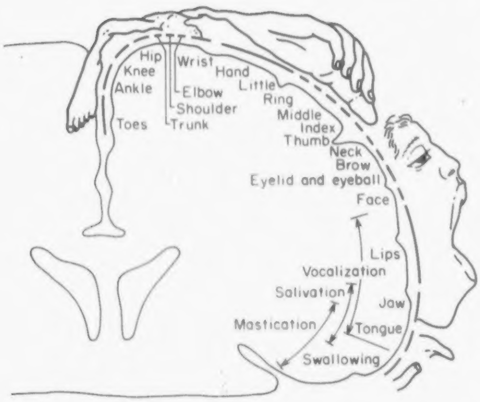

FIG. 1. The human motor cortex shows a disproportionately greater development of areas associated with hands and faces. (Modified from Bodmer and Cavalli-Sforza, 1976, after W. Penfield and Associates.)

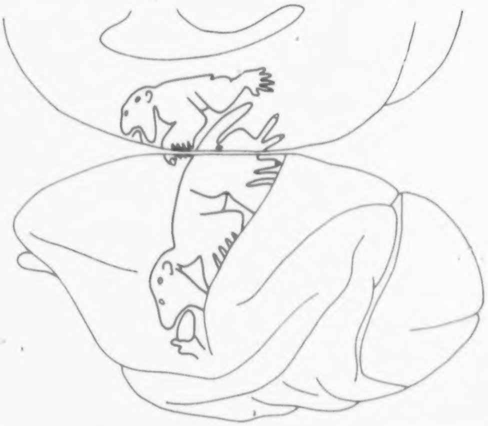

FIG. 2. In contrast with the human motor cortex (Fig. 1), that of the monkey does not show such a disproportionately greater development of areas associated with hands and feet. (Modified from C. N. Woolsey in *Biological and Biochemical Bases of Behavior*, edited by H. F. Harlow and C. N. Woolsey, Univ. of Wisconsin Press, 1958.)

indicating that animals learn a great deal of skills and social customs from their parents or from the social group.

HOMO AS A CULTURAL ANIMAL

There is no question that the evolution of humans has generated an organism which can produce a very rich culture. It is quite interesting to study the maps of localization in the human brain of specific sensation and muscle areas that are involved in skills typically connected with culture, in particular those that use hands or voice. There are some classical drawings made from brain maps in which organs controlled by specific zones of the cerebral cortex are shown as parts of the body of a little man, a homunculus (Fig. 1). This Homunculus has enormous lips and tongue and an enormous hand. All the rest of the body is essentially much less developed at the level of neurological structures. If one looks at the brain maps of other organisms, including primates, one finds no such development of the cerebral areas controlling organs most deeply involved in our cultural adaptation (Fig. 2).

The monstrous development of mouth and hands in these human brain maps clearly emphasizes the importance of the neurological mechanisms that make our cultural adaptation possible. There have to be other parts of the brain that take part in cultural mechanisms, but there are not equally good localization maps for them. We are well aware that the size of the human brain relative to the total body is much higher than that of other primates, mammals, or in general higher animals.

It is worth recalling some of the main stages through which this remarkable cultural animal has developed. We can give reasonable dates only for some. The development of stone tools and their use has been one of the earliest in the human species, and there are proofs that two to three million years ago primitive stone tools were probably used for killing and processing large animals. Fire is also very old. One date of 1.4 billion years from Kenya has been questioned; another date from Czechoslovakia of 750,000 years ago is more satisfactory. For many other technical and intellectual developments we have only late dates that tell us when these skills were already relatively highly developed.

Language is of paramount importance in human cultural evolution. Between 50,000 and 100,000 years ago the species that we call *Homo sapiens sapiens* (or modern man) was already in existence, and during

TABLE 1. *Main steps in human cultural evolution.*

Stone tools	2,000,000 to 3,000,000*
Fire	1,400,000 to 750,000
Speech	?>100,000 to 50,000
Clothing	>25,000
Art	>16,000
Food production	10,000
Writing	5,500

* Estimated time of onset in years before present.

the last 50,000 years it spread over a large part of the earth from a still uncertain place of origin, somewhere in west Asia or perhaps even Africa. Fifty thousand years ago human language must have been about as perfect as today, because when humans spread to the whole earth they carried with them the capacity of using and developing very sophisticated languages. There have been claims that the anatomical structure of the larynx in Neanderthal, the predecessor of modern man, was not as well developed as to make it possible to have speech as good as we have today (Wang, 1979). But there have been criticisms of this hypothesis which must be considered today with great caution. The importance of language of a degree of development as high as it is today in our species cannot be overestimated because it is clear that cultural behavior depends greatly on the possibility of communication. The development of writing, which has made communication possible at long distances in space and time is much more recent, and is not older than 5,500 years. Its onset corresponds with the beginning of history.

It is worth remembering three other activities that have been of considerable importance in the evolution of man. One is the development of clothes, which has certainly contributed to the conquest of climate. There is an example of tailored cloth from 25,000 years ago in the USSR. The development of art has been another characteristic feature of human behavior. One finds already excellent examples of sculpture and painting from 20,000 to 30,000 years ago. The cave of Lascaux in southwest France is dated about 15,000 years ago and contains an unrivaled series of masterpieces that convince us these artists were as sophisticated and powerful as some of the best artists of today. Finally, one initiative which started about 10,000 years ago in the Middle East and also developed independently in other parts of the earth, Central and South America and the southeast of Asia, is the production of food. This technological "innovation" is actually a complex ensemble of innovations which involve the development and domestication of many plants (and animals in the Middle East) and processing of their products. Agriculture was responsible for increasing the population density on earth by a factor of over 1,000 times. Table 1 summarizes the dates of these major steps of human cultural evolution. Many more dates can be found in Calder (1983).

ANALOGIES OF BIOLOGICAL AND CULTURAL EVOLUTION

History is often the best key to understanding social, political and economic situations of the world or parts of it. Similarly biologists usually have to recur to the study of evolution in order to fully understand what is going on today. One would expect to find equal interest in evolutionary analysis among students of culture.

In this century, a revolt has taken place among social and cultural anthropologists against some old and certainly unacceptable nineteenth century attempts at the study of cultural evolution (see White, 1959). Today acceptance of the word evolution is reserved for a very small facet, that of the increase of complexity in political systems. What biologists would more generally call evolution is somewhat demeaningly referred to as "cultural change." Among linguists, there is even less interest, with the notable exception of recent work by Wang (1977). Only the history of technologies has been given considerable attention, although also here one rarely finds studies on general factors of change.

Given the strong evolutionary background in modern biology, it is not surprising that biologists have shown an interest in cultural evolution. Attempts at explaining cultural change on the basis of analogies between biological and cultural evolution have been made repeatedly and usually by biologists. My own interest in culture developed after coming in contact with African Pygmies, hunter-gatherers of the African tropical forest. The customs of these people were so strikingly different from any that I was used to, that my curiosity was stimulated to try and understand something more of mechanisms of cultural change (Cavalli-Sforza, 1971). Even a superficial reading of the ethnographic literature convinced me that the process of cultural change can be explained with factors which are formally very similar to those that one finds in the study of biological evolution. The latter, however, has been so much more a subject of attention and consideration by many students that the study of biological evolution is a discipline of its own, and is backed by a mathematical theory unusually sophisticated in comparison with other biological fields.

We are quite familiar in biology with the idea that transmissible information is subject to changes which we call mutation. We know mutations are rare but it is inevitable that sometimes the copy of a model is not perfect. We know that most mutations are deleterious to the organism, and this must be basically the reason why the mutation rate is kept low by natural selection. We also know that a presumably small fraction of some mutations must be advantageous and such mutants have spread to the population by the mechanism of natural selection over what is usually a fairly high number of generations. Natural selection, of course, also eliminates automatically the deleterious mutations. There is also, we believe today (Kimura, 1983), a certain number of mutations that are neither deleterious nor advantageous. Their relative importance is harder to assess even now, but is certainly not negligible. They are called "selectively neutral" and are more easily subject to the action of chance in the form of random genetic drift.

It is worth noting that the word *drift* in biology has a different meaning from that which is used in linguistics. In the latter discipline drift means a *trend* towards certain changes, for instance the replacement of some vowels by other vowels which seems to follow partially predetermined routes. In biology, as we all know, drift means the *random* fluctuation of gene frequencies from one generation to the other, due to sampling errors arising in the formation of every new generation. In fact, only a small fraction of gametes produced by the individuals of a population mature to become parents in the next generation. The fewer these parents are in a given population, the more chances for random fluctuations of the relative frequencies of the existing forms of a gene from one generation to the other. In biology we are also familiar with the idea that with a very small number of evolutionary factors, essentially the three that were just named—mutation, natural selection and drift—one can explain a great deal of evolutionary phenomena. It is customary to add a fourth factor to these three, migration, usually meant to be the exchange of individuals between groups. Migration tends to buffer the effects of drift, which would in the absence of migration tend to generate extreme differences between different populations completely isolated one from the other. There is no question that one can recognize factors like these four in cultural evolution. The source of change is of course very different from biological mutation, and the material that is transmitted is very different in culture and in biology. We know that DNA, genes, or chromosomes are the material that is transmitted in biology and carries genetic information from one generation to the next. In culture it is ideas and techniques and skills and behaviors which are transmitted from one generation to another. There is only a very formal and abstract analogy between genes and ideas. They are both essentially blueprints, but physically are of a very different nature. For many decades the physical nature of genes was quite obscure, but now great progress has been made towards its elucidation. We still have great difficulties in defining the physical nature of ideas, and have to wait for better knowledge of the neurological mechanisms responsible for the thinking process before we can say something more definite for the physical (biological) structures behind ideas. Also for this reason it is extremely difficult to devise a unit of cultural evolution, while it has been rela-

TABLE 2. *Comparison of factors of biological and cultural evolution.*

	Biological	Cultural
Units evolving	DNA, nucleotides, genes, chromosomes	Languages, ideas, rules, beliefs, tools, etc.
Source of variation	Mutation (copy error)	Innovation and/or copy error
Transmission of information	Parent-to-child	Many different mechanisms
Choice of "mutants" by	Natural selection	Ourselves (cultural selection)
Migration	"Gene flow," etc.	Borrowing (of words, etc.)
Chance (drift)	Very slow in large populations. Faster in small and isolated populations	Effect can be very strong, especially when one person's decisions are influential for many others.

tively easy to identify units like genes that change in genetic evolution.

Some of the analogies that I have cited are summarized in Table 2 (see also Cavalli-Sforza, 1971). Different words are used in the different disciplines for what is essentially the same concept. Novelty is introduced in biology by mutation, and in culture by innovation. The latter is usually not as random as the former. In fact, innovation is frequently the result of an intentional improvement of a particular situation or solution of a problem. Even so there remains a certain element of randomness also in innovation, but it would be difficult to discuss this point further in this place (for a longer discussion of the subject see Cavalli-Sforza and Feldman, 1981). It is interesting to note that the analogies shown in Table 2 have been found independently by a number of people. It was pointed out to me, for instance, that conclusions very similar to Table 2 were described earlier by a group of anthropologists and sociologists (Gerard *et al.*, 1956). Similar considerations have been made later by several other people. The earliest analysis to my knowledge is probably also the most dramatic presentation of the analogy between biological and cultural evolution. It was written by R. A. Fisher when he was a student at Cambridge.

The nature of the transmissible units and mechanisms of change listed in Table 2 are not the only differences that exist between biological and cultural situations. Another very important one is the difference existing between the two in mechanisms of transmission. It is because of this difference that cultural adaptation is much faster, potentially at least, than biological adaptation by natural selection. It thus represents a major reason why cultural adaptation can be particularly useful, such as situations of fast and drastic change of environmental conditions, or interactions with other individuals. In biology transmission is almost exclusively vertical (*i.e.*, from parent to child). Under biological transmission, a population tends to remain absolutely unchanged over generations, because parent-child transmission is highly conservative, and ensures persistence generation after generation of the biological *status quo*, including all the existing variation between individuals. There is no tendency for a population to change biologically unless one or more of the factors of evolution—mutation, selection and drift—are operating. But cultural transmission is quite different. It is extremely variable in the sense that some mechanisms are responsible for very fast change and at the opposite extreme others are responsible for a very high conservation. Thus mechanisms of cultural transmission can be the key for both conservation as well as fast change observed in the evolution of culture.

TYPES OF CULTURAL TRANSMISSION

It is clear from what we have said that cultural transmission may deserve special study, being probably the major mechanism by which culture acquires one of its most peculiar characters, namely its flexibility. But the mechanism of cultural transmission also makes it possible, if necessary, to have conservation almost as strong or stronger than for genes.

My colleague Marc Feldman and I (Cavalli-Sforza and Feldman, 1981) have dedicated considerable time and effort to predict by the use of suitable mathematical models the properties of cultural transmission, studying in particular those mechanisms that observation around us shows as the most frequent.

We have found it useful to model four major mechanisms of cultural transmission, briefly explained in what follows and also represented in Figure 3. The first mechanism we call vertical (a name borrowed from epidemiology) and is the transmission from parent to child. One or both parents may contribute to the teaching of children. It is clear that these mechanisms are present in humans and in animals, and in some conditions may represent the greatest portion of all the teaching and learning taking place.

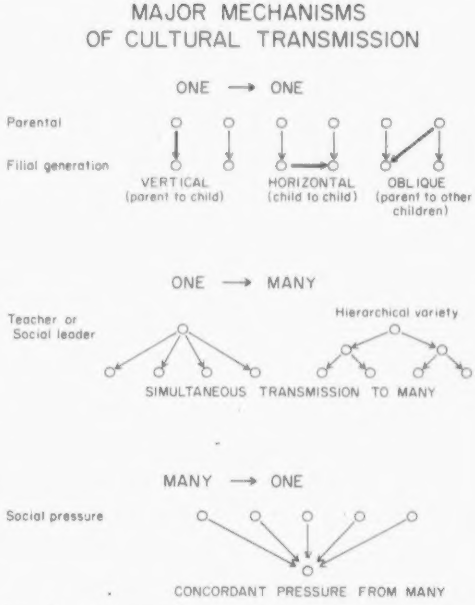

FIG. 3. Major mechanisms of cultural transmission.

A second very important mechanism is one often considered most characteristic of cultural transmission although it is by no means the only one. It is the mechanism by which exchange of information goes on between two unrelated people, say from A to B, after which it is transferred from B to C, from C to D, and so on. This is very similar to the process of transmission of infectious diseases, and has been studied mathematically for understanding the generation of epidemics. It is therefore not surprising that this mechanism can be represented by the same mathematical equations that have been put forward in epidemiology even if there is a great difference, of course, between the diffusion of an infectious disease and of an innovation. But an essential phenomenon of cultural transmission, even when diffusion is extremely fast, is that the cultural knowledge thus reached will often persist generation after generation. (This happens also with infectious disease and distinguishes "endemics" from "epidemics".) Because of this, we therefore have to always pay attention to the age structure of the population. Probably cultural transmission from older to younger people, even if it is not the only direction in which transmission takes place, is the dominant direction. But there is also transmission between age peers. We have found it useful from the point of view of developing mathematical models to simplify the age structure to the extreme by considering the population subdivided in distinct generations. Then transmission between two unrelated people can take place (1) between people of the same generation, and we have reserved the adjective *horizontal* for this type of transmission; or (2) between a member of the former generation and a non-related member of the next generation (which we have called *oblique* transmission). Relatedness must be mentioned because we want to distinguish oblique transmission from vertical.

A third very important model of cultural transmission can be considered as a special type of horizontal transmission in which there is only one transmitter but there are many transmittees. We can call this mode "one-to-many." The obvious consequence of this model is that transmission to a whole population can be much faster and in fact even instantaneous. Mass media have made this process particularly rapid and capable of encompassing at once enormous numbers of individuals. In the past, in the absence of mass media, extension to great numbers of individuals often demanded establishment of hierarchical ladders so that transmission would first lead from one person to two or more individuals, each of which would then in turn transmit to further groups. With many steps in this ladder one could reach very large numbers of individuals, though in more time and probably generating more noise in transmission than in a true one-to-many transmission. Clearly, one-to-many is the fastest mechanism of cultural transmission.

A fourth model is in a way the opposite of the one just mentioned: many individuals influence a single transmittee and all act in concert so that they exercise a concordant pressure on that individual. Often transmitters are of the older generation, and the same action is exerted by the same transmitters on other transmittees of the next generation, so that the whole of the next generation is under a barrage of social pressure from people of the older generation, and each individual is under the influence of many. This is the essence of social pressure and we refer to this mechanism by that name and also by the term "many-to-one."

EXAMPLES AND PROPERTIES OF THE VARIOUS MECHANISMS OF CULTURAL TRANSMISSION

The study of cultural transmission is inevitably much more simple in humans than in animals, because of the ease of observation and because of the greater wealth of material. There have been studies of innovations and their diffusions and of the social and geographic networks through which propagation takes place. A successful innovation tends to increase according to a logistic pattern. That is, the curve of increase in the frequency with which the innovation spreads in a population is at the beginning almost exponential, and progressively slows down its rate of increase until it reaches a flat portion, an asymptote. This levelling is reached when the diffusion is complete, or also at an intermediate level. The whole curve has an S-shaped form. This kinetic behavior is extremely similar to that of an epidemic. Technological innovations are by far the best studied cases (Fig. 4) but there are also historical examples of the spread of certain rules in language, at the level of syntax, pronunciation and lexicon (Wang, 1977). The process of acquisition of an innovation can often be shown to be made of at least two stages: in the first stage awareness takes place, and in the second acceptance. Both phases may have a kinetic similar to that of a logistic. A new technology can replace an old one, and the competition between the two has also been shown to have logistic behavior. An elegant example was supplied by Marchetti and Nakicenovic (1979), who have studied among others the replacement of sources of energy (see Fig. 5) beginning with wood, switching to coal, then to natural gas and other forms of energy (including futuristic ones). At the beginning the proportion of energy coming from a particular source increases as a logistic, reaches a maximum and begins to descend again as a logistic under competition from another source. In the figure, the abscissa is time and the ordinate is a function $\log(f)/(1 - f)$ of the proportion, f, of energy coming from one source (or in other cases, of the proportion of people using a particular type of technology). This is a well known function, also called a logit, which transforms a logistic to a straight line, an ascending one if the particular form of cultural trait studied is successfully replacing an old one, and a descending line when the opposite is true. An exponential increase can be very fast, a logistic increase can also be fast (especially at the beginning when it is almost exponential). These are typical cultural diffusion examples.

For many other cultural traits, however, there is substantial conservation. We know that some religions have been more or less unchanged over thousands of years. Conservation can sometimes be explained by biological determination, sometimes by the mechanism of transmission when this is of highly conservative nature like vertical or many-to-one. A third one is the dependence from other cultural rules which are themselves highly conserved. An important factor in transmission is the age of the

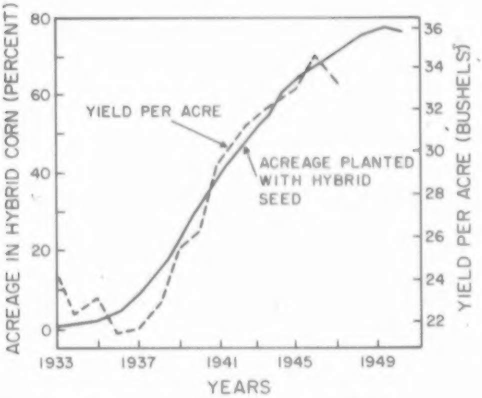

FIG. 4. The transition to the use of hybrid corn. As the proportion of total acreage planted in hybrid corn in the U.S.A. has increased, the average yield has gone up correspondingly. (Modified from P. C. Manglesdorf in *Genetics in the Twentieth Century*, edited by L. C. Dunn, Macmillan, 1951.)

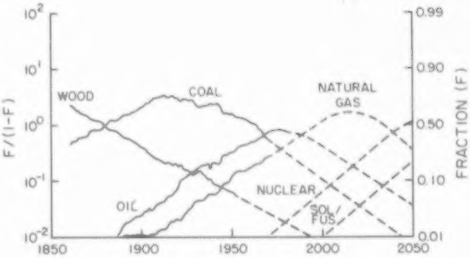

FIG. 5. Trends in the use of different sources of energy. Continuous lines show actual use; dotted lines are predictions. (Modified from Marchetti and Nakicenovic, 1979.)

recipient. The extreme example is that of imprinting in birds. A newly hatched bird is extremely sensitive in the first twenty-four hours to certain stimuli that can be fixed as accepted as the mother. Even inanimate objects that are observed in that period by a newly-hatched bird may be followed like a mother in later months. In classical imprinting there is a sensitive period which does not last very long, during which subjects can be imprinted very specifically by suitable stimuli, and the imprinting will last for all life. There are no equally sharp situations in humans, but certainly there are ages that are more sensitive, especially in some respects, and ages in which certain influences are more important and profound. Languages are learned mostly and most easily between 2 and 12 years of age. After puberty most individuals have lost the ability of learning the pronunciation of new sounds, perhaps because the necessary skill of perceiving differences in sounds has decreased drastically. Although there is rarely a total learning disability at certain ages, there are substantial differences in the speed with which things of different nature are learned at different ages. Factors tied to age, like sensitive periods, etc. are likely to be of great importance in the culture.

In different societies there are great differences in chances of exposure to the various modes of cultural transmission, and as we have seen that these have different effects on conservation in time and in space and also on the individual variation that is permitted, the cultural effects will be quite different depending on the mode of transmission that will prevail for a particular trait. In our society the effect of parents is restricted to early ages and some specific spheres of knowledge and behavior, but the majority of learning is taking place at school or in the environment of age peers. In an analysis of Stanford students for a variety of traits having to do with everyday life and ranging from religion, politics, and entertainment, to beliefs and superstitions and everyday customs, sharp differences were found in influence of parents for these various types of traits (Fig. 6, from Cavalli-Sforza *et al.*, 1981). In particular religious behavior was very deeply influenced by parents, and more so by the mother, although some social aspects of religion like the frequency with which religious ceremonies are attended is equally influenced by father and mother. Politics was also influenced by parents, while for most other traits the effect of parents was sometimes negligible or sometimes detectable but small. There were indications from twin studies that the observed similarity of parents and children for religion and politics were not of biological origin, but rather cultural. Possibly attitudes towards religion are determined at a very early age and

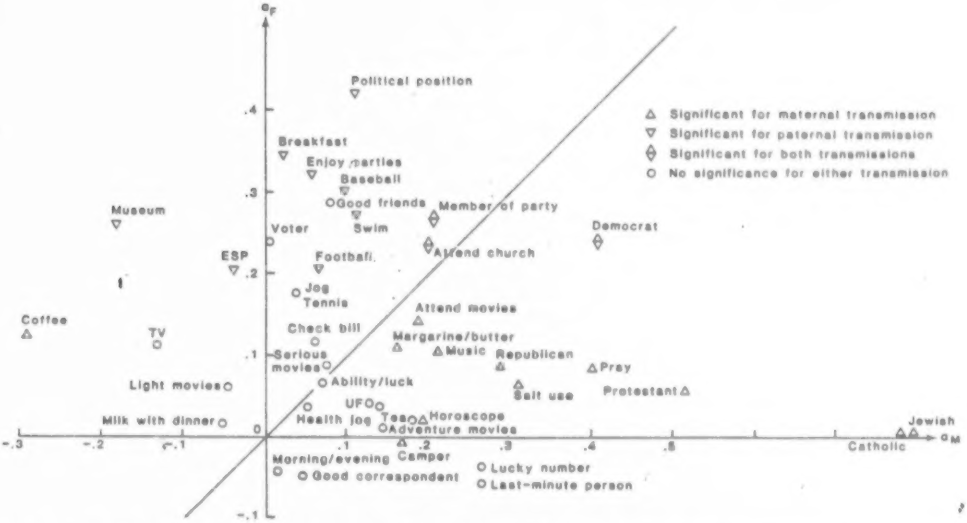

FIG. 6. Coefficients of paternal (α^F, vertical axis) and maternal (α^M, horizontal axis) estimated for 41 traits. The 45° line corresponds to equal influence of father and mother (from Cavalli-Sforza *et al.*, 1982, Science 218:19–27 [copyright 1982 by the AAAS] which can be consulted for details).

the mother has most assuredly access to this part of the psychology of the child.

At the other extreme of the socio-economic complexity, a population of African hunter-gatherers was examined for the role taken by parents and other people in the transmission of specific items of importance in daily life (Hewlett and Cavalli-Sforza, 1986). The analysis was centered in particular on survival skills and on social behavior. The range of cultural traits examined is inevitably very different in this hunter-gatherer society compared with that of Stanford students. The sharp contrast observed between the importance of parental teaching in the former compared with the latter society remains nevertheless striking. Among Pygmies the most important contacts until puberty are with parents. Social groups are extremely small, and there are not many age peers, but parents take a very active part in the teaching of all survival skills. The few skills which were transmitted in other ways were those relative to social life, including dances, which are an important part of social exchanges, and social traits of the kind are also taught by the social group. It is interesting to note that both vertical transmission and social group pressure are very highly conservative mechanisms and this may contribute to explain why hunter-gatherers groups are still in existence in their environmental niches. Whenever their original environment is still available and capable of supporting them, hunter-gatherers have shown considerable resistance to acculturation. The only example of a trait that was found to diffuse in the "infectious" way was a particular technology, the building and use of the crossbow. This came to Pygmies from the outside fairly recently and is still diffusing at the present day in the Pygmy society of the Central African Republic and Cameroon.

The one-to-many mode of transmission is also responsible for heavy random drift in cultural change. By this mechanism, the decisions and choices of a single person can be followed or adopted by a great number of individuals. Transmitters in cultural drift take the place of parents in biological transmission; the number of parents is the determining factor in biological drift, the number of transmitters that in cultural drift. When the transmitter is a single person, drift is at its maximum.

There are few examples of studies of

transmission, but they are likely to help us understand cultural evolution, given the inevitable influence that the mode of transmission has on the rate of change. Another important problem is that of the relation between genetics and culture. There can be genetic variation for traits that are involved in social behavior and in the exploitation and creation of new technology and so on. The interaction between this potential genetic variation and the forces that shape culture is an extremely interesting subject for study. Unfortunately it is also extremely difficult. The distinction of genetic transmission and cultural transmission has baffled and, worse, misled many scientists. The numerous errors made in the study of the genetic determination of the intelligence quotient are a splendid example of the caution that should be exercised when investigating this specific field. In principle, the only way to separate the effects of genes from those of environment and its cultural transmission is by the study of adopted children. Unfortunately adopted children are few and there are many complications derived from the ages at which they are adopted and even more by the origin and distribution of children for adoption. Even adoption studies, therefore, are not flawless and at the moment many problems of behavioral genetics in humans where no experimentation is possible have to be declared too difficult for our means of investigation. Probably the mapping of chromosomes will provide a great number of genetic markers which may well make it more easy to study the genetics of some behavioral traits and will give us some feeling of security in deciding these issues. At the moment one should accept with extreme caution any statement on the inheritance of behavioral traits and in principle trust only those conclusions that are supported by means of sound adoption studies.

The study of culture in humans and animals has only now begun. It is the best chance perhaps for tuning in to interdisciplinary studies, in that a variety of different disciplines ranging from anthropology and sociology to genetics are a necessary basis for significant results. There are many important discoveries in store for critical and enthusiastic scientists.

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Geneticists and Race[1]

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SYNOPSIS. During the twentieth century, geneticists have dramatically changed their assessments of the biological and social consequences of human race differences and race crossing. In the first quarter of the century, most geneticists thought that human races differed hereditarily by important mental as well as physical differences and that wide race crosses were biologically and socially harmful. The period from 1925 to the outbreak of World War II saw no change in geneticists' views on hereditary mental differences between human races, but a shift to agnosticism on the issue of wide race crosses. By the early 1950s, geneticists generally argued that wide race crosses were at worst biologically harmless, but still held to earlier beliefs about hereditary mental differences between races. The final period from 1951 to the present has witnessed the shift to agnosticism on the issue of hereditary mental differences between races. The changes in geneticists' assessments of race differences and race crossing were caused by increased understanding of the complex relationship between genes and environment and by cultural changes.

INTRODUCTION

The current assessment of geneticists regarding the issue of genetics and race is easily stated at the outset. "There is no convincing evidence as to whether there is or is not an appreciable genetic difference in intelligence between races" (Genetics Society of America Resolution on Genetics, Race and Intelligence, 1976). "There is no evidence that race mixture produces disadvantageous results from a biological point of view" (UNESCO Statement on the Nature of Race and Race Differences, 1951). These two direct statements accurately represent the current state of scientific knowledge on genetics and race.

In isolation, however, these statements reveal little about the reasons for the intense controversies over genetics and race that have raged in the twentieth century or about the contributions that geneticists have made to the controversies. In this essay, which is a necessarily brief summary of a book that I am writing on geneticists and race, I will attempt to place the current assessment of geneticists into historical perspective, perhaps the best way to understand the significance of their current position on genetics and race.

This essay builds directly upon the historical framework provided in John Moore's introductory essay, which should be read first. The essay begins with the nineteenth century background before turning to developments in the twentieth century, which can be conveniently divided into the following four periods. The first, from 1900 to 1924, saw the dominance of the beliefs that human races differed hereditarily by important mental as well as physical traits, and that crosses between widely different races were biologically harmful. The second, from 1925 to 1939, saw no change in geneticists' attitudes about race differences but a shift to agnosticism on the issue of wide race crosses. In the third period, 1940 to 1951, geneticists reversed their views on race crossing and argued that wide race crosses were at worst biologically harmless, but most geneticists still held to older views about hereditary racial differences in mentality. The final period, 1951 to the present, witnessed the shift to agnosticism on the issue of hereditary mental differences between races.

THE NINETEENTH CENTURY BACKGROUND

Between 1860 and 1900 Americans and Europeans felt a new urgency about problems associated with race differences. The U.S. Civil War and the freeing of slaves precipitated an outpouring of writings about race. Europeans divided up the entire continent of Africa and increased imperialistic activities throughout the world, dramatically increasing their interactions with other races. Race-related social issues grew accordingly.

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Biological conceptions of race differences and race crossing did not begin with the rediscovery of Mendelian heredity in 1900. Many of the ideas expressed by geneticists in the early twentieth century were earlier expressed by biologists in the late nineteenth century. Indeed, the views of geneticists on the question of race in the early heyday of their new field were inevitably drawn from the cultural context and scientific knowledge of the late nineteenth century. Despite a wide range of criteria for judging the taxonomic status of racial groups in animals, nineteenth century biologists agreed that Australian aborigines, African blacks, South American Indians, orientals, and white Europeans were of different racial groupings.

The foremost thing to understand about the attitudes of nineteenth century biologists is that they were in general far more hereditarian in their outlook than are biologists today. We know vastly more about mechanisms of heredity and have documented a huge number of cases of inheritance. But geneticists today also know a great deal about clearly measurable individual differences that are inherited weakly if at all and are well aware that the whole concept of inheritance (heritability) may depend strongly upon the particular environment in which the measurement is made. Thus geneticists generally know that they must be very careful in generalizing from within-group heritability (measured in a single environment) to heritability of differences in the same character between groups that may have been subjected to different environments. Compared to Charles Darwin, Edward O. Wilson and Arthur R. Jensen, both of whom now have widespread reputations as ardent hereditarians regarding human behavior, must be ranked as strong environmentalists.

Charles Darwin

Darwin was certainly the most influential biologist of the nineteenth century. On the voyage of the *Beagle* (December 1831 to October 1836) he observed African blacks, South American Indians (including the Fuegians), South Sea islanders, and Australian aborigines among others and he had no doubt that they were distinguishable races of humans and that their differences in physical characters, from facial features and hair to height and skin color, were inherited. He also thought the evidence for hereditary mental differences between human races was incontrovertible. When he first saw native Fuegians on the east coast of Tierra del Fuego in December 1832, he wrote a friend:

> I have seen nothing which more completely astonished me than the first sight of a savage. It was a naked Fuegian, his long hair blowing about, his face besmeared with paint . . . . Standing on a rock he uttered tones and made gesticulations, than which the cries of domestic animals are far more intelligible. (Darwin, 1887, I, pp. 255–256)

Recalling this same incident in his *Journal of Researches*, Darwin commented:

> I do not believe it is possible to describe or paint the difference between the savage and civilized man. It is the difference between a wild and tame animal: and part of the interest in beholding a savage, is the same which would lead every one to desire to see the lion in his desert, the tiger tearing his prey in the jungle, the rhinocerous on the wide plain, or the hippopotamus wallowing in the mud of some African river. (Darwin, 1839, p. 606)

Darwin clearly believed that the mental differences between civilized man (white Europeans in particular) and savage races had evolved primarily through natural selection and were in large part hereditary. As Darwin wrote to his friend Charles Lyell,

> I suppose that you do not doubt that the intellectual powers are as important for the welfare of each being as corporeal structure; if so, I can see no difficulty in the most intellectual individuals of a species being continually selected; and the intellect of the new species' thus

> improved, aided probably by effects of inherited mental exercise. I look at this process as now going on with the races of man; the less intellectual races being exterminated. (Darwin, 1887, II, p. 211)

In his lifetime Darwin witnessed the elimination of the Tasmanian aborigines. He was so certain that white Europeans would eliminate the lower human races that he predicted the gap between the anthropoid apes and humans would become larger. He thought the only possible escape from extinction for many of the lower races was to cross with other more intellectual races, much as some biologists now recommend the cross-breeding of some rare raptors with more numerous closely related varieties.

At the same time, he was aware that cultural forces could significantly alter behavioral patterns. He frequently argued that slavery, which he detested, was a major cause for the degradation of the native Africans. In his *Journal of Researches* from the voyage of the *Beagle*, Darwin tells of one incident that showed him how significantly slavery could depress the mental state of a human being. He was on a ferry with a Negro man, a slave, who was described to him as "uncommonly stupid." Darwin gestured with his hands to communicate better; the man, thinking Darwin was going to hit him, cringed in preparation for a blow. Darwin recalled: "I shall never forget my feelings of surprise, disgust, and shame, at seeing a great powerful man afraid even to ward off a blow, directed, as he thought, at his face. This man had been trained to a degradation lower than the slavery of the most helpless animal" (Darwin, 1839, p. 28). To counteract the common opinion about the very low intelligence and capabilities of Negroes, Darwin on many occasions expressed his higher opinion of them in his writings and personal correspondence.

Defending African blacks against the views of pro-slavery Englishmen did not, however, mean that Darwin believed there were no significant hereditary mental differences between blacks and white Europeans. Darwin had himself observed the results of an experiment to turn Fuegians into civilized persons. On board the *Beagle* were four English speaking Fuegians, whom Captain Fitzroy had brought to England on a previous voyage. These Fuegians had acquired many civilized traits in addition to the language, and Fitzroy hoped that when returned to their native land they would foment the spread of civilized habits through the population of Tierra del Fuego. Darwin observed the differences between the "civilized" and uncivilized Fuegians and accordingly believed that the capacity for civilization was significantly present in Fuegians. But the "civilized" Fuegians quickly reverted to primitive life when left for a year in their native land, as Darwin observed when the *Beagle* next visited Tierra del Fuego. This he found disappointing but hardly surprising. He commented that the Fuegians "skill in some respects may be compared to the instincts of animals; for it is not improved by experience," and that "nature by making habit omnipotent, and its effects hereditary, has fitted the Fuegian to the climate and the productions of his country" (Darwin, 1839, pp. 236–237).

Darwin summarized his views of race differences in his *Descent of Man.* There is, he said,

> No doubt that the various races, when carefully compared and measured, differ much from each other—as in the texture of the hair, the relative proportions of all parts of the body, the capacity of the lungs, the form and capacity of the skull, and even in the convolutions of the brain. But it would be an endless task to specify the numerous points of structural difference. The races differ also in constitution, in acclimatization, and in liability to certain diseases. Their mental characteristics are likewise very distinct; chiefly as it would appear in their emotional, but partly in their intellectual faculties. Every one who has had the opportunity of comparison, must have been struck with the contrast between the taciturn, even morose, aborigines of South America and the light-hearted, talkative negroes. There is a nearly sim-

> ilar contrast between the Malays and the Papuans, who live under the same physical conditions, and are separated from each other only by a narrow space of sea. (Darwin, 1871, I, pp. 216–217)

Darwin harbored no antagonism toward any human race. He believed all humans should treat each other with respect and compassion. Yet he was certain that no amount of humanistic feeling or environmental manipulation could possibly remove entirely those racial differences erected by nature. There was no use pretending human races had equal mental capacities.

One must appreciate that Darwin saw the question of racial differences in mentality from a very different perspective than do geneticists at present. Two aspects of Darwin's background are especially important in relation to his observations. First, he knew a great deal about animal and plant breeding and he relied heavily upon the opinions of breeders. Even more than the general population, breeders believed that virtually all differences in physical features or behavior had a hereditary component. That was why they had been able to produce a diversity of domesticated animals, all with their different physiques and characteristic behavior patterns. Second, he belonged to a culture that emphasized hereditarian views, in particular that Caucasians were superior to all other races. Darwin observed differences in mental abilities to perform certain tasks. He concluded that these differences resulted from hereditary differences. For Darwin and his contemporaries, the scientific evidence for hereditary mental differences between human races was overwhelming. In his day, this conclusion was good science; indeed, the best.

Thomas Henry Huxley

Like Darwin, Thomas Henry Huxley was strongly opposed to slavery and championed the liberal view that all people should be freed from any fetters that traditional society had placed upon them. In 1865, as the Civil War in the United States was ending, he wrote an essay entitled "Emancipation—Black and White." He argued strongly that blacks and white women should be given the same opportunities in society as white men.

When freed of social fetters, would women and blacks equal the achievements of white men? Huxley answered:

> It may be quite true that some negroes are better than some white men; but no rational man, cognizant of the facts, believes that the average negro is the equal, still less the superior, of the average white man. And, if this be true, it is simply incredible that, when all his disabilities are removed, and our prognathous relative has a fair field and no favour, as well as no oppressor, he will be able to compete successfully with his bigger-brained and smaller-jawed rival, in a contest which is to be carried on by thoughts and not by bites. The highest places in the hierarchy of civilization will assuredly not be within the reach of our dusky cousins, though it is by no means necessary that they should be restricted to the lowest.
>
> The big chests, the massive brains, the vigourous muscles and stout frames, of the best men will carry the day, whenever it is worth their while to contest the prizes of life with the best women. (T. H. Huxley, 1871, pp. 20–21, 25)

Huxley's conclusion might easily have been said by a geneticist of today. "The duty of man is to see that not a grain is piled upon that load beyond what Nature imposes; that injustice is not added to inequality" (p. 26). Darwin would have agreed. So far as treatment under the law is concerned, the position of Huxley and Darwin is very similar to that of Martin Luther King. But the truth is that Darwin and Huxley also believed there was no chance blacks or women could on the average equal the achievements of white men. I cannot emphasize too strongly that both Darwin and Huxley clearly understood that the social policy they advocated stemmed from the kind of society they wanted (one with legal equality), not from their scientific knowledge of hereditary mental differences between races.

Francis Galton and the distribution of intelligence among races

Even before Darwin published the *Descent of Man* most biologists in England, on the Continent, and in America believed races to differ hereditarily in intelligence. The more interesting problem for them was to judge degrees of intelligence in races. What was needed was a quantitative, scientific method for comparing intelligence in different races. Darwin's half-cousin, Francis Galton, invented that method.

Galton, an Englishman, traveled widely in north and south Africa between 1845 and 1852. He observed many African tribes and became very interested in what he called "the mental peculiarities of different races." He was much influenced by Charles Darwin's works on evolution and heredity, especially the *Variation of Animals and Plants Under Domestication,* which Darwin published in 1868. Galton began a study of the inheritance of mental traits in the mid-1860s, culminating in the publication of his book *Hereditary Genius* in 1869. In that book Galton presented an analysis of the mathematical distribution of intelligence in human populations, and he proposed a method for quantitatively comparing intelligence in different races.

Reasoning from a study of the distribution of heights of French soldiers by the Belgian statistician Quetelet, who found a normal (or "bell curve") distribution, Galton argued that "if this be the case with stature, then it will be true as regards every other physical feature—as circumference of head, size of brain, weight of grey matter, number of brain fibres, etc.; and thence, by a step on which no physiologist will hesitate, as regards mental capacity" (Galton, 1869, pp. 31–32). Having established in earlier chapters that about 250 men per million in England fit his definition of eminent, Galton constructed a normal distributive curve for one million men divided into fourteen grades, the top two of which (plus the upper tail of the distribution, in this case containing one individual) contained 248 men. Table 1 is based on this analysis (Galton, 1869, p. 34). The table was quantitative and exact. Galton urged the reader to understand

> that the numbers of men in the several classes in my table depend on no uncertain hypothesis. They are determined by the assured law of deviations from an average. It is an absolute fact that if we pick out of each million the one man who is naturally the ablest, and also the one man who is the most stupid, and divide the remaining 999,998 men into fourteen classes, the average ability in each being separated from that of its neighbors by *equal grades,* then the numbers in each of those classes will, on the average of many millions, be as is stated in the table. The table may be applied to special, just as truly as to general ability. It would be true for every examination that brought out natural gifts, whether held in painting, in music, or in statesmanship. The proportions between the different classes would be identical in all these cases, although the classes would be made up of different individuals, according as the examination differed in its purport. (Galton, 1869, pp. 34–35)

Of course Galton's table had to be correct, supposing intelligence was normally distributed; but he had no evidence for that except for his suggestive analogy with distribution of height. A second problem that Galton minimized here was the identification of the individuals who belonged in each category. But one element of Galton's genius was an ability to forge ahead, brushing major and minor difficulties aside.

Using his table for a working model for the distribution of intelligence, Galton assessed the comparative intellectual worth of different races. Like Darwin, Wallace, and Huxley, Galton rejected the simplistic thesis that all members of one race might be inferior to all members of another. When the well-known anthropologist James Hunt delivered a paper on the Negro at the ethnology section of the British Association Meeting of 1863 and claimed that no "pure Negro ever advances further in intellect than an intelligent European boy of fourteen years of age," Galton, as sum-

TABLE 1. *Classification of men according to their natural gifts.*

Grades of natural ability, separated by equal intervals		Numbers of men comprised in the several grades of natural ability, whether in respect to their general powers, or to special aptitudes							
				In total male population of the United Kingdom, say 15 millions, of the undermentioned ages					
Below average	Above average	Proportionate, viz. one in	In each million of the same age	20–30	30–40	40–50	50–60	60–70	70–80
a	A	4	256,791	641,000	495,000	391,000	268,000	171,000	77,000
b	B	6	161,279	409,000	312,000	246,000	168,000	107,000	48,000
c	C	16	63,563	161,000	123,000	97,000	66,000	42,000	19,000
d	D	64	15,696	39,800	30,300	23,900	16,400	10,400	4,700
e	E	413	2,423	6,100	4,700	3,700	2,520	1,600	729
f	F	4,300	233	590	450	355	243	155	70
g	G	79,000	14	35	27	21	15	9	4
x all grades below g	X all grades above G	1,000,000	1	3	2	2	2	—	—
		On either side of average	500,000	1,268,000	964,000	761,000	521,000	332,000	149,000
		Total, both sides	1,000,000	2,536,000	1,928,000	1,522,000	1,042,000	664,000	298,000

The proportions of men living at different ages are calculated from the proportions that are true for England and Wales. (Census 1861, Appendix, p. 107.)

Example.—The class F contains 1 in every 4,300 men. In other words, there are 233 of that class in each million of men. The same is true of class f. In the whole United Kingdom there are 590 men of class F (and the same number of f) between the ages of 20 and 30; 450 between the ages of 30 and 40; and so on.

marized by the *Anthropological Review*, replied that "the Negro, though on the average extremely base, was by no means a member of a race lying at a dead level. On the contrary, it had the capacity of frequently producing able men capable of taking an equal position with Europeans. The fact of a race being distinguished by the diversity of its members was well known to the ethnologists." In short, Galton believed that the intelligence of a person was not determined by his race, but that races differed in average intelligence. Galton, like almost all twentieth century geneticists who addressed problems of race differences, was well aware that differences within a racial group were far greater than the differences between racial groups. Thus in this respect Galton may be classified as a populational thinker rather than a racial typologist (a distinction popularized by Ernst Mayr).

Assuming that all races had normal distributions of intelligence, Galton proceeded to compare the intelligences of Englishmen, Negroes, and the Athenians of fifth century B.C. He claimed the intellectual standard of Negroes was about two grades below that of Englishmen for the following reasons. (1) The best Negroes, like Toussaint l'Ouverture, were at least two grades below the best Englishmen; (2) Negroes produced some men "considerably raised above the average of whites"; (3) White travelers who met native Negro chiefs rarely felt inferior to them (What happened when travelers met native chiefs? Said Galton, "The result is familar enough—the white traveller almost invariably holds his own in their presence. It is seldom that we hear of a white traveller meeting with a black chief whom he feels to be the better man. I have often discussed this subject with competent persons, and can only recall a few cases of the inferiority of the white man,—certainly not more than might be ascribed to an average actual difference of three grades, of which one may be due to the relative demerits of native education, and the remaining two to a difference in natural gifts."); and (4) Negroes produced many half-witted men. Next Galton produced similar evidence demonstrating that the Athenians had possessed average ability, "on the lowest possible estimate, very nearly two grades higher than our own—that is, about as much as our race is above that of the African negro." Australian aborigines were at least one grade below Negroes. And Lowland Scotch and English North-country men were "decidedly a fraction of a grade superior to that of the ordinary English." The essential argument was that all grades of intelligence, except the extremes, occurred in all of these "races," but the numbers of individuals in each grade differed in accordance with the average of the race (Galton, 1869, pp. 338–339, 340, 342).

Galton's evidence for his thesis about racial differences in intelligence appears ludicrous from the modern perspective. But Galton, and many of his readers, believed he was making quantitative scientific judgments where others had prevously made subjective guesses.

Like Wallace and Darwin, Galton believed that average differences of intelligence between classes or races were of much social importance. "If we could raise the average standard of our race only one grade, what vast changes would be produced?" From his table reproduced above (fourth column) Galton pointed out that instead of 233 men of high eminence in grade F, there would now be 2,423, an increase of more than a factor of ten. And the numbers of those of higher intelligence would show an even greater increase. This increase of talented men would be a great boon to society, Galton said, because "we know how intimately the course of events is dependent upon the thoughts of a few illustrious men." Consequently, he believed it "most essential to the well-being of future generations, that the average standard of ability of the present time should be raised" (Galton, 1869, pp. 343–344). Civilization was rapidly becoming industrialized and complicated, and more intelligent people were needed to carry out the tasks of society. An added benefit would be the elimination of the least intelligent members of society. It is hardly surprising that when Galton invented the science of eugenics, defined by him as "giving the more suitable races or strains of blood a better chance of prevailing speedily over the less suitable," he could also say: "There exists a sentiment, for the most part quite unreasonable, against the gradual extinction of an inferior race" (Galton, 1883, pp. 25, 308).

Conclusion

I have presented the views of Darwin, Huxley, and Galton in this section because their views on race differences fairly represent the general attitude not only in England but in Europe, Russia, America, and elsewhere. Moreover, all three were highly respected and influential scientists. The power of their views can be assessed by the reaction to them by a scientist such as Franz Boas, one of the most influential anthropologists of the early twentieth century. He was a Jew born and educated in Germany, where his bad experiences with race prejudice as a youth led him to detest ideas of race inequality. When he turned his attention seriously to the study of man, Boas would have liked to argue that no significant hereditary mental differences existed between races. In 1894 Boas was Vice-President of the anthropological section of the American Association for the Advancement of Science and at the annual meeting he delivered a major address entitled "Human Faculty as Determined by Race." He began the address by challenging the common belief that the white race had to be hereditarily superior to other races because their civilization was demonstrably superior. Other races had not received the same advantages as whites, he argued; we should not conclude that primitive races were incapable of rising to higher levels of civilization.

The scientific arguments, especially those of Galton, compelled Boas, against his own humanitarian desires, to conclude that significant hereditary differences in average mental capacity probably did exist between races. He concluded:

> It does not seem probable that the minds of races which show variations in their anatomical structure should act in exactly the same manner. Differences of structure must be accompanied by differences of function, physiological as well as psychological; and, as we found clear evidence of difference in structure between the races, so we must anticipate that differences in mental characteristics will be found. Thus, a smaller size or lesser number of nervous elements would probably entail loss of mental energy, and paucity of connections in the central nervous system would produce sluggishness of the mind. As stated before, it seems probable that some differences of this character will be found between the white and negro, for instance, but they have not been proved yet. (Boas, 1894, p. 323)

Explicitly using Galton's model, Boas also concluded that all human races had sufficiently similar capacities that all were capable of attaining high levels of civilization:

> The average faculty of the white race is found to the same degree in a large proportion of individuals of all other races, and although it is probable that some of these races may not produce as large a proportion of great men as our own race, there is no reason to suppose that they are unable to reach the level of civilization represented by the bulk of our own people. (Boas, 1894, p. 327)

Twenty-five years after the "Human Faculty" paper, after researchers found a very low correlation between IQ and cranial measurements, Boas was delighted to be rid of his earlier position. But in 1894 the scientific evidence for hereditary racial differences in mental capacity seemed overwhelming. Common sense observation demonstrated to most white observers that Fuegians or Australian aborigines or Negroes had less intelligence than whites. The great evolutionary biologists, led by Darwin, all believed that races differed hereditarily in average levels of intelligence. Galton had furnished a quantitative model that neatly incorporated this belief. Thus in the late nineteenth century the person who denied inherent racial differences in intelligence was, by the highest scientific standards of the time, simply being unscientific.

Stephen Jay Gould in his book *The Mis-*

measure of Man (1981) has strongly emphasized the role played by craniometry in the scientific arguments about hereditary differences in intelligence between races during the nineteenth century. I would emphasize here that many other lines of scientific evidence led in the same direction. Darwin, Huxley, and Galton all believed they were making reasonable deductions from abundant evidence ranging from inheritance in domestic animals to observed behavior patterns exhibited by the Fuegians transplanted to England or African tribesmen in their native settings. It was not bad science by the standards of the time that led to the scientific conception of hereditary mental differences between races, it was good science. By present standards, of course, the evidence, arguments and conclusions of Darwin, Huxley, and Galton would be bad science.

GENETICS AND RACE: THE RISE OF MENDELIAN GENETICS

After the rediscovery of Mendelian heredity in 1900 and geneticists successfully solved previously inscrutable problems, their confidence in the wide applicability and significance of genetics grew accordingly. The high spirits of the time were expressed by the English geneticist R. C. Punnett in his little textbook, *Mendelism*. First published in 1905, it was quickly sold out and a new edition called for in 1907. In the preface to the second edition Punnett was enthusiastic about the progress shown since the first edition and commented: "As year follows year, and experiment succeeds experiment, there is forced upon us a sense of what it all may come to signify for ourselves, of the tremendous powers of control that a knowledge of heredity implies." His concluding words in the book were more explicit. "The facts of heredity," he said, "speak with no uncertain voice":

> Education is to man what manure is to the pea. The educated are in themselves the better for it, but their experience will alter not one jot the irrevocable nature of their offspring. Permanent progress is a question of breeding rather than of pedagogics: a matter of gametes, not of training. As our knowledge of heredity clears, and the mists of superstition are dispelled, there grows upon us with an ever-increasing and relentless force the conviction that the creature is not made but born. (Punnett, 1907, pp. 80–81)

Ten years later, Punnett was more skeptical about the possibility of genetic cures for social problems. But in 1907 he expressed the hopes of many geneticists who found very appealing the prospect that genetics might provide scientific cures for some pressing social problems.

Human heredity presented special problems for the Mendelians. Generation times were long, accurate records poor, and matings impossible to arrange. Most of the early genetical analysis of human heredity therefore was directed toward distinct pathological characters such as albinism or alkaptonuria. Geneticists consciously decided to concentrate their efforts upon more tractable organisms because, as Edward Murray East at Harvard later said, "the laws ruling the inheritance of the denizens of the garden and the inmates of the stable were found to be applicable to prince and potentate as well" (East, 1923, p. vi).

The social problems associated with race differences and race crossing seemed obviously to have a strong genetic component. Thus problems associated with race inevitably attracted the attention of those geneticists interested in the social implications of their work. By the early 1920s, a clear consensus had emerged from these geneticists regarding the issues of race differences and race crossing.

With the rapidly increasing knowledge of heredity in general, and of the inheritance of abnormal traits in humans in particular, came the rise of the eugenics movement. Riding the crest of genetic discoveries, eugenists wished to apply the newfound knowledge to the genetical improvement of human populations. The possibilities for genetic improvement seemed both great and feasible. In addition to eliminating medical defects, many eugenists hoped to eliminate problems like criminality and feeblemindedness. In many countries geneticists lent their prestige and support to the early eugenics movement. I will not here examine the eugenics movement or geneticists involvement in it because several excellent studies are readily available, the most recent being that of Kevles (1985). The eugenics movement is, however, the backdrop from which most geneticists spoke about race. Geneticists who wrote and lectured about race in the first quarter of the twentieth century generally treated it as a subdivision of their larger interest in the eugenic improvement of humans.

Again, I will emphasize that geneticists did not set the cultural tone for analysis of the issues involving race. For example, the great eleventh edition of the *Encyclopaedia Britannica* stated flatly that "Mentally the negro is inferior to the white," and only barely softened this statement by adding, "But though the mental inferiority of the negro to the white or yellow races is a fact, it has often been exaggerated; the negro is largely the creature of his environment" (Vol. 19, p. 344). Geneticists reflected this larger cultural view, but they also augmented it with their scientific justifications.

Charles Benedict Davenport

Davenport was the first American geneticist to devote his primary attention to human genetics. Although aware of the small amount of data available, he believed (along with most other geneticists) that the growing evidence from other animals could be meaningfully extended to humans. Beginning in 1907, Davenport and his wife Gertrude began publishing serious research on human heredity: on eye color (1907), hair form (1908), hair color (1909), and skin pigment (1910). Although many of the Davenports' genetic hypotheses were later modified by more exact research, the papers established them as major students of human heredity. Every contemporary genetics textbook cited these papers, including those published in England and Germany; the Davenports stood out in a field where little research was being conducted on the inheritance of normal characters in humans. Later historians have tended to condemn Davenport for sloppy and almost fraudulent research on human heredity, but they have not taken adequate account of these early papers or the high regard other geneticists held for them.

In 1911, Davenport published his book, *Heredity in Relation to Eugenics*, which contained almost all that was then known of human genetics. The purpose of the book was to interest educated lay persons in eugenics. Realizing that eugenics had to be founded upon exact knowledge of human heredity, Davenport attempted to convince the reader that geneticists knew a great deal about human heredity. He included every possible hereditary trait, with little critical distinction. Thus he presented albinism, alkaptonuria, musical ability, and feeblemindedness all as simple Mendelian recessives. Compelling genetic evidence for the first two was available, but not of course for the latter two. From the vantage point of modern human genetics, *Heredity in Relation to Eugenics* appears naive and overinflated; but in 1911 most geneticists found the book congenial even if they disagreed on particulars. Davenport was clearly the leading geneticist studying human heredity in the world at the time.

He was the first geneticist to publish extensively on race differences and race crossing. To understand Davenport's views on race it is necessary to first examine a crucial aspect of his general view of Mendelian heredity. He thought that Mendelian factors often controlled specific morphological or mental characters. Thus eye color was generally inherited independently of skin color in human crosses. In 1917 Davenport published a long article on the inheritance of stature in man, where he argued that many of the components of stature were inherited separately. For example, he thought an individual could inherit long arms from one parent and short legs from another. In the same year Davenport published a paper on human race crossing in which he argued that crossing between two distinct human races could be expected to yield disharmonious combinations of characters. Breeding a tall race with a short one could produce some children with "large frames and inadequate viscera" or "children of short stature with too large circulatory apparatus" (Davenport, 1917, p. 366).

Perhaps more important in Davenport's view were the possible mental disharmonies that might arise from race crossing. He, like other geneticists, believed that races differed hereditarily in many mental characters, including intelligence, temperament, and emotions. And he also thought that the components of these aspects of mentality could be inherited separately. Thus he concluded that mental disharmonies as well as physical ones were to be expected in race crosses.

The color line

In 1918 the first edition of *Applied Eugenics* appeared. Written by Roswell Hill Johnson, who had studied under Davenport, and Paul Popenoe, the editor of *The Journal of Heredity*, this book would become the most widely used textbook on eugenics in America for more than two decades (a second edition appeared in 1933). The first six chapters outlined the current knowledge of heredity in humans (drawing of course from Davenport's book) and presented the argument for eugenic selection. The next fourteen chapters examined the practical means by which society could encourage eugenic selection with recommendations for social policy.

The inevitable chapter on race, entitled "The Color Line," argued that racial antipathy, visible wherever two distinct human races came into contact, was not simple bigotry but a hereditary behavior pattern evolved by natural selection as a mechanism protecting races from miscegenation. Popenoe and Johnson analyzed in particular the issues related to blacks and whites in America.

Negroes were inferior to whites, they argued. The evidence they cited for this assertion was that Negroes had made no original contribution to world civilization; they had never risen much above barbarism in Africa; they did little better when transplanted to Haiti; they had not achieved white standards in America; and their disease resistance was inferior to that of whites in America (although this situation was reversed in Africa). The new IQ tests revealed that Negroes scored significantly worse than whites. They concluded:

> From the foregoing different kinds of evidence, we feel justified in concluding that the Negro race differs greatly from the white race, mentally as well as physically, and that in many respects it may be said to be inferior, when tested by the requirements of modern civilization and progress, with particular reference to North America. (Popenoe and Johnson, 1918, pp. 291–292)

Popenoe and Johnson next turned to the question of race crossing between blacks and whites. Mulattoes, they claimed, were intermediate between the two parent races in color and intelligence; thus, "in general the white race loses and the Negro gains from miscegenation." For this reason they "unhesitatingly condemn miscegenation." But what of the argument that the surest way to elevate the Negro was through crossing with whites? They answered in Galtonian terms:

> To insure racial and social progress, nothing will take the place of leadership, of genius. A race of nothing but mediocrities will stand still, or very nearly so; but a race of mediocrities with a good supply of men of exceptional ability and energy at the top, will make progress in discovery, invention, and organization, which is generally recognized as progressive evolution.
>
> If the level of the white race be lowered, it will hurt that race and be of little help to the Negro. If the white race be kept at such a level that its productivity of men of talent will be at a maximum, everyone will progress; for the Negro benefits just as the white does from every forward step in science and art, in industry and politics. (Popenoe and Johnson, 1918, p. 293)

Here was Galton's conclusion again, but now supported by the data and wording of twentieth century genetics and quantitative psychology. Popenoe and Johnson ended their chapter on race with a strong exhortation for laws and taboos against intermarriage between blacks and whites: "Miscegenation can only lead to unhappiness under present social conditions and must, we believe, under *any* social conditions be biologically wrong" (p. 297).

Popenoe and Johnson were not working geneticists but each had been the editor of *The Journal of Heredity* (for a short time they were joint editors), which published many articles by the leading geneticists. For example, Sewall Wright published there an outstanding series of eleven articles on color inheritance in mammals in 1917 and 1918. Popenoe and Johnson were very sensitive about being in touch with the views of geneticists.

For the purposes of this essay the most important aspect of *Applied Eugenics* is its reception by geneticists. So far as I can tell, geneticists welcomed the book. To my knowledge, no geneticist wrote a negative review of it. I spoke to Paul Popenoe on the telephone in 1971 and asked him about both the sources he and Johnson used to write the race chapter (he said that Johnson wrote the first draft of the chapter) and what reception geneticists gave the chapter. He said that they tried throughout the book to adhere to uncontroversial positions widely held by geneticists. In a written response to my question about the reception geneticists gave the chapter, he replied that he could "not recall that any geneticists disapproved of that chapter. It was definitely in line with the views of the majority, so far as I then knew" (Popenoe to Provine, 1971).

One might reasonably be tempted to dismiss Popenoe's evaluation as merely a self-serving historical veil. Actually, the contemporary evidence completely bears out his assessment. Not one geneticist publicly challenged the use of genetics to support the racial assessments or recommended policies. *Applied Eugenics* sold very well and went through several printings in the first edition and was used as the major textbook for eugenics courses at many universities, some of which were taught by geneticists. By contrast, the same ideas published in 1969 would certainly have been vigorously and justly attacked by leading geneticists.

Edward Murray East and the genetics of race

Although Popenoe and Johnson had both studied genetics, neither was a research geneticist. Davenport was respected by many of his colleagues and students but his work on human genetics was clearly tentative when compared to genetic research on more tractable organisms. Edward Murray East of Harvard's Bussey Institution, on the other hand, was deservedly one of the most highly respected research geneticists in the world. He also had greater influence than any other geneticist in America on issues of the implications of genetics for social and cultural policy from 1919 until the mid-1930s.

East began his academic career as an expert in corn breeding. His work on corn ranged from attempts to change the protein content to the study of multifactorial Mendelian inheritance. He was also a pioneer in the development of hybrid corn. After he came to Harvard in 1909, East became interested in the genetics of tobacco, and he became the world's expert on the inheritance of self-sterility alleles in that plant and in others. He had many distinguished graduate students at the Bussey Institution and was widely respected in the genetics community as one of the most careful and exacting geneticists anywhere. Thus when East began to write about the relation of genetics to social concerns, editors and publishers were eager to have his manuscripts and other geneticists read his publications.

During World War I, East worked seriously on the question of world agricultural planning for the United States government. He became intensely interested in questions related to the interaction of genetics and social policy and considered it his duty to speak out on the prospects and dangers that he saw on the horizon. For the rest of his life, East devoted much attention to the issues of overpopulation and what he viewed as eugenic decline. Race differences, race crossing, and social aspects of race relations, all socially volatile issues, naturally attracted his attention.

Immediately after the war, East and his former student, Donald F. Jones, published a technical book entitled *Inbreeding and Outbreeding* in the prestigious Lippincott biological monographs series edited by Jacques Loeb and Thomas Hunt Morgan. East did not let the opportunity to raise social issues pass so easily—he added two chapters on humans and gave the book the extended title: *Inbreeding and Outbreeding: Their Genetic and Sociological Significance.* The book was an enormous success, required reading for all geneticists, and widely praised.

The final chapter was devoted entirely to discussion of race differences and race crossing. East chose this topic because "the world faces increasing amounts of race amalgamation, and there is naturally an acute interest in race problems" (East and Jones, 1919, p. 248) and because he believed that genetics could rationally be applied to the problems. From the genetics of other organisms, he deduced that human race crosses were likely to be of two types. Those between closely related races, such as the white races of Europe, could be expected to produce beneficial results. But East could see two possible genetical objections to wide human race crosses. First, Mendelian segregation would "break apart those compatible physical and mental qualities which have established a smoothly operating whole in each race by hundreds of generations of natural selection" (p. 253). Second, he thought that because race crosses generally produced intermediate physical and mental traits, the cross between blacks and whites should be avoided: "It seems an unnecessary accompaniment to humane treatment, an illogical extension of altruism . . . to seek to elevate the black race at the cost of lowering the white" (p. 254). East had no doubt that blacks were genetically mentally inferior to whites on the average. "In reality the negro is inferior to the white. This is not hypothesis or supposition; it is a crude statement of actual fact" (p. 253).

East's first objection to wide race crosses was that given by Davenport. The second was a direct reiteration of the objection raised most recently by Popenoe and Johnson, whose book East cited for evidence concerning the mental inferiority of blacks. Thus these objections to wide race crosses now had the clear approval of a top research geneticist who claimed that he was examining the issue objectively in accordance with known genetic facts, and East had established himself in the book as the world's expert on the biological facts of crossbreeding.

Geneticists reacted very favorably to *Inbreeding and Outbreeding.* Raymond Pearl, a prominent geneticist at Johns Hopkins University who in the 1920s was a strong opponent of the "Nordic enthusiasts" like Madison Grant and Lothropp Stoddard, reviewed the book for *Science* and heaped praise upon it, including the last two chapters, which must, he wrote, "fairly be regarded as among the sanest and most cogent arguments for the integral incorporation of eugenic ideas and ideals into the conduct of social and political affairs of life . . . . There is a refreshing absence of blind and blatant propaganda" (Pearl, 1920, p. 415).

After 1919, East published three books (East, 1923, 1927, 1931) and more than twenty articles on genetics and society. The first book, *Mankind at the Crossroads,* went through several large printings. Throughout all these publications, East maintained the same views about race differences and race crossing. In the period 1919 to 1935, he was certainly the most visible American geneticist writing about such issues and was considered by many intellectuals as the spokesman for the genetics community.

East was not a simple racist who argued that all blacks were mentally inferior to all whites. He was a population biologist, not a "typologist." East specifically ridiculed the biology of the popular racists such as Madison Grant, Seth Humphrey, and Lothropp Stoddard. Although these writers claimed to have based their assertions upon modern genetics, East denied this vehemently and classified them as "race dogmatists," whose belief that one race was completely superior to another was false biology. He sketched the difference between a biologist's point of view and that of a race dogmatist:

> The one forbids racial crossing because of an indefensible belief in the general superiority of all the individuals of one race over all the individuals of another; the other advises against racial crossing even between widely separated races of equal capacity simply because the operation of the heredity mechanism holds

> out only a negligible prospect of good results against a high probability of bad results through disturbing the balanced whole of each component. Both recognize differences in racial levels or averages, but the biologist realizes what an immense amount of overlapping there is. He sees how small is the gap between the efficiency levels of each race as a whole, and how great is the chasm between the superior and inferior extremes within the race, even though each race may have exclusive possession of certain hereditary units. (East, 1923, pp.131–132)

Furthermore, East was a staunch supporter of civil liberties for every individual. He was indignant about discrimination against blacks on trains and restaurants. He exclaimed that such discriminatory actions were "the gaucheries of a provincial people, on a par with the guffaws of a troop of yokels who see a well-dressed man for the first time" (East, 1927, p. 181). He clearly distinguished between biological equality and social equality under the law. But East, the population biologist who believed in civil rights for all, is the same person who concluded that "the negro as a whole is possessed of undesirable transmissible qualities both physical and mental, which seem to justify not only a line but a wide gulf to be fixed permanently between it and the white race" (East, 1923, p. 133).

Conclusion

In 1924 there could be little doubt in the minds of those who might be interested in what geneticists had to say about race differences and race crossing. From the published literature they could only conclude that geneticists possessed scientific evidence indicating strongly that human races differed hereditarily in intelligence and that wide human race crosses were dangerous at best, and probably should be avoided.

It is so easy from the current perspective to look back upon these geneticists, condemn them for their obvious racism, and brand their science as pseudo-science or worse. If they presented the same views today, we would be entirely justified in these assessments. But an objective historical perspective indicates that their views represented the mainstream rather than the fringe of geneticists, and that the great majority of geneticists believed, along with East and Davenport, that human races differed hereditarily in mentality. This conclusion was good science at the time, though not at the present.

GENETICISTS AND RACE, 1924–1939

In the mid-1920s Davenport and his associate Morris Steggerda conducted extensive research on blacks, whites and hybrids between them in Jamaica, examining physical characters and, using mental tests, intelligence (Davenport, 1928*a*, *b*; Davenport and Steggerda, 1929). In his report of this research to *Science*, Davenport stated that the evidence he had gathered in Jamaica was unequivocal in pointing to hereditary mental differences between blacks and whites: "We are driven to the conclusion that there is a constitutional, hereditary, genetical basis for the difference between the two races in mental tests. We have to conclude that there are racial differences in mental tests" (Davenport, 1928*b*, p. 628). They also concluded that the hybrids show both physical and mental disharmonies, but they admitted that their evidence was meager and that "the results merely propose an hypothesis and do not warrant a conclusion" (Davenport and Steggerda, 1929, p. 472).

The reaction of other geneticists to Davenport's conclusions is instructive. Many, like Herbert Spencer Jennings, a distinguished geneticist at Johns Hopkins University (and a former student of Davenport's), accepted Davenport's conclusions, as Jennings demonstrated in his book *The Biological Basis of Human Behavior* (1930). Others, led by William Castle of Harvard (also a former student of Davenport's), disagreed with Davenport's conclusions about the supposed disharmonies exhibited by the hybrids. Castle published in *Science* a strong and famous attack upon both Davenport and Jennings in 1930:

> We like to think of the Negro as an infe-

> rior. We like to think of Negro-white crosses as a degradation of the white race. We look for evidence in support of the idea and try to persuade ourselves that we have found it even when the resemblance is very slight. The honestly made records of Davenport and Steggerda tell a very different story about hybrid Jamaicans from that which Davenport and Jennings tell about them in broad sweeping statements. The former will never reach the ears of eugenics propagandists and Congressional committees; the latter will be with us as the bogey man of pure-race enthusiasts for the next hundred years. (Castle, 1930, p. 605)

Castle's *Science* article and this passage in particular has been hailed by Ashley Montagu and others as the precursor of the non-racist views that geneticists would express publicly only after Nazi atrocities were understood after World War II. Nothing Castle wrote has been so widely or favorably cited by other authors.

Just as in the case of East, however, historical perspective requires a rather different interpretation. Jennings had actually been a more vocal and activist opponent of the eugenists than had Castle. And Castle in 1924 had clearly stated that the white race had "less skin pigment and more intelligence" than blacks, and that mulattoes were intermediate in both characters (Castle, 1924, p. 366). East objected to black-white crosses on the grounds that the average intelligence of the whites would be reduced, resulting in fewer individuals of outstanding mental qualities. Castle agreed, but argued that this was a *social* rather than *biological* objection to wide race crosses, a characterization that East did not accept. Moreover, in the fourth edition of his widely used book, *Genetics and Eugenics,* published in the same year as his article in *Science* quoted above, Castle stated that "wide racial crosses among men seem on the whole undesirable" because the *particular combination* of characters found in each race would be broken apart (this passage had remained unchanged since the first edition in 1916: Castle, 1916, p. 233). Castle believed that the breaking-up of these particular combinations did not lead to disharmonious combinations, but the crosses might be opposed for social reasons. The real disagreement Castle had with Jennings and Davenport concerned their view of disharmonious race crossing, and Castle had evidence from rabbits that physical disharmonies simply did not occur in the way they had predicted. Castle agreed with them that blacks were, in a populational sense, mentally inferior to whites. (For a fascinating and somewhat different view of geneticists and race in the 1920s and 1930s see Glass, 1986.)

Castle's view that physical disharmonies were not to be expected from wide race crosses were borne out by Davenport's data and by a number of other studies of race crosses by geneticists and physical anthropologists. The most important of these were by L. C. Dunn and A. M. Tozzer (1928) on race crossing in Hawaii, by R. R. Gates (1928) on Amerindian crosses in Canada, by H. L. Shapiro (1929) on the descendants from the *Bounty* on Pitcairn Island, and by M. Herskovits (1928) on black-white crosses in the United States. There was, of course, still the possibility that more careful analyses, such as of fetal deaths or post-natal problems, might reveal problems with race crossing. Mental disharmonies and hormonal unbalances were also possible problems as Davenport frequently asserted. But the evidence for disharmonies from human race crossing was beginning to look very thin by the early 1930s.

By the late 1930s, the fear of disastrous physical disharmonies resulting from wide race crosses had almost disappeared among geneticists. Still, they worried that other disharmonies might arise. The German geneticist Fritz Lenz argued that crosses between Caucasians and Jews resulted in disharmonious mentality (Baur *et al.*, 1931). As geneticists became aware of Nazi race doctrines (which much resembled the simple-minded theories of Madison Grant and Lothropp Stoddard, whose works were translated into German), they reacted very negatively and published books and articles debunking Nazi race theories. Perhaps the two most significant examples were *We Europeans* (1936) by Julian Huxley and A.

C. Haddon and *Heredity and Politics* by J. B. S. Haldane. Although attacking Nazi race doctrines severely in these works, both Huxley and Haldane stopped short of denying that there might be hereditary mental differences between human races or that race mixture held no biological dangers. Haldane wrote:

> I would urge the extraordinary importance of a scientific study of the effects of racial crossing for the future of the British Commonwealth. Until such a study has been accomplished, and it is a study that will take generations to complete, we are not, I think, justified in any dogmatism as to the effect of racial crossing . . . . I am sure that the fact of our ignorance is a deplorable one which we ought to remedy. (Haldane, 1938, pp. 184–185)

And Huxley declared:

> In human genetics, the most important immediate problem is to my mind that of "race crossing." . . . The question whether certain race crosses produce "disharmonious" results needs more adequate exploration. Social implications must also be borne in mind in considering this subject. (Huxley, 1938*b*, p. 294)

East died in the same year as these quotes from Huxley and Haldane, and there remained no geneticist who continued the dire warnings about wide race crosses that he had sounded for more than fifteen years.

During the period 1924–1939, many geneticists kept the same attitude toward hereditary mental differences between races as had been expressed by East or Davenport. Thus in the first edition of his important textbook *Heredity*, A. Franklin Shull stated that "numerous studies, involving mental tests, school records, industrial success, and the like, agree in showing that the negro is mentally, at least, inferior to the whites" (Shull, 1926, p. 249). The same statement appeared unchanged in the third edition of 1938. Other geneticists' attitudes about hereditary mental differences between races, however, began to change, at least in emphasis, during the years 1924–1939. Before 1924 geneticists concluded from the *scientific* evidence that there were hereditary mental differences between races. Beginning in 1925, however, some geneticists began to argue that the scientific evidence was inconclusive. Among the first of these geneticists were Thomas Hunt Morgan (1925, pp. 205–207) and his former student Alexander Weinstein (1933). But the absence of positive evidence did not mean that geneticists believed there were no hereditary mental differences between races. They continued to believe that such differences did in fact exist but that the evidence was still forthcoming. This was very much like their attitude toward "genes" during the same period of time. Geneticists knew that the scientific evidence for material genes was inconclusive but they believed that future research would justify their belief in material genes; and of course this strong hunch later proved true.

By 1939, with the ugly consequences of Nazi race doctrines already beginning to be understood outside of Germany, most geneticists, even if they believed the scientific evidence for hereditary mental differences between races to be conclusive, did not say so in published documents. The prevailing attitude seen in print is well represented by the following two passages, one from Julian Huxley in England and the other from Samuel J. Holmes at the University of California at Berkeley. In his Galton Lecture of 1936 Huxley first pointed out the danger from unscientific theories of race differences: "The dangers of pseudo-science in these matters are being illustrated on a large scale, and with the accompaniment of much individual suffering and political danger, in present-day Germany. The Nazi racial theory is a mere rationalization of Germanic nationalism on the one hand and anti-Semitism on the other" (Huxley, 1938*a*, p. 17). Then he presented his views about race differences:

> Man as an animal organism is unique in several respects: and one of them is his abnormal range of genetic variability . . . .
>
> It would be most unlikely that this

> variability should be evenly distributed between different social and ethnic groups. As regards the latter, indeed, the existence of marked genetic differences in physical characters (as between yellow, black, white and brown) make it *prima facie* likely that differences in intelligence and temperament exist also. For instance, I regard it as wholly probable that true negroes have a somewhat lower average intelligence than the whites or yellows. But neither this nor any other eugenically significant point of racial difference has yet been scientifically established. (pp. 18–19).

Writing in *Science,* a very prestigious forum, Holmes reacted against the cultural anthropologists and others who, in the face of the Nazi specter, had begun to state publicly that modern science had proved the mental equality of human races:

> It has become the fashion to refer to race differences in mentality as if it were now demonstrated that no such differences exist, or, at least, that they are negligible in extent. In the light of our meager and unsatisfactory knowledge and the alternative possibilities of interpretation which existing data permit, this is, I think, a very unscientific position. (Holmes, 1939, p. 353)

The historical evidence is overwhelming that the great majority of geneticists before World War II continued to believe that races differed hereditarily in intelligence, and in particular that African blacks were in a populational sense less intelligent than whites.

Aftermath of Nazi atrocities: The UNESCO statements on race of 1950–1951

News of the Nazi atrocities repulsed people everywhere. No biologist wanted to give support to Nazi-like race doctrines, including assertions about hereditary mental inequality of races. After the war, only two geneticists, C. D. Darlington in England and R. R. Gates in the United States, made public statements indicating a belief in hereditary mental differences between human races, and both were dismissed as radical hereditarians by other geneticists at the time. Biologists and anthropologists published many books and papers attacking Nazi race theories and racism in general. The tone was completely different than before the war. Any possible differences between races in mentality were minimized. A. F. Shull, whose textbook before the war had stated flatly that "the negro is mentally, at least, inferior to the whites" revised this section in the fourth (1947) edition to read:

> The lack of any suitable measure (of race differences in mentality) is particularly evident when claims of the "superiority" or "inferiority" of any race are made. In such claims, some one has to decide how to balance, let us say, literary ability against artistic, scientific bent against philosophy. Races unquestionably differ in such matters, and perhaps at any particular time and place one type of ability would work out more advantageously than another. But such needs change more rapidly than races can change, so that even if "good" and "bad" could be correctly determined at any moment the judgement would not long remain correct. A still more serious fault of such decisions, however, lies in the plain fact that people who have made them in the past have expected to benefit economically from them. One can scarcely avoid the conclusion that estimates of racial worth are simply rationalization; some one is trying to brand as true that which he wishes were true, and acceptance of which as true would for the moment benefit him. (Shull, 1947, p. 276)

One would be hard-pressed to guess that this was written by the same person as the earlier statement. But it is important to notice in this passage that Shull did not retreat from the belief that races "unquestionably" differed in their hereditary mental capacities. His dilemma in writing about race in the light of the Nazi atrocities was to maintain his scientific beliefs while at the same time rejecting Nazi-like social action based upon the belief that races differed in mental capacity.

The dilemma between objective science and correct moral position on the question of race was particularly brought into focus by the debates surrounding the UNESCO Statements on Race in 1951 and 1952. The Preamble to the Constitution of UNESCO stated that

> the great and terrible war which has now ended was a war made possible by the denial of the democratic principles of the dignity, equality and mutual respect of men, and by the propagation, in their place, through ignorance and prejudice, of the doctrine of the inequality of men and races.

The mandate given to the Director General of UNESCO was to adopt "a program of disseminating scientific facts designed to remove what is generally known as racial prejudice" and "to study and collect scientific materials concerning questions of race . . . to give wide diffusion to the scientific information collected . . . to prepare an educational campaign based upon this information." In other words, UNESCO was supposed to fight racism worldwide by promulgating science and truth. It would not do for UNESCO to issue statements saying that scientists think that races differ hereditarily in mental capacities and therefore they should be treated equally. The dilemma was how to design the appropriate objective science to yield the desired moral conclusion.

In 1949 the Department of Social Sciences of UNESCO convened the first committee to draw up the first UNESCO Statement on Race. Several geneticists were invited but either declined or were unable to attend, leaving a committee of sociologists and cultural anthropologists. Led strongly by rapporteur M. F. Ashley Montagu, an anthropologist with a wide reputation as an opponent of racism, the committee drew up a document that appeared to serve the purposes of UNESCO. The statement as published and distributed worldwide contained the following assertions:

> For all practical purposes "race" is not so much a biological phenomenon as a social myth.
>
> The scientific evidence indicates that the range of mental capacities in all ethnic groups is much the same.
>
> There is no evidence that race mixture as such produces bad results from the biological point of view.
>
> Biological studies lend support to the ethic of universal brotherhood; for man is born with drives toward cooperation, and unless these drives are satisfied, men and nations alike fall ill.

The problem was that the science was supposed to be unassailable, but geneticists and physical anthropologists immediately attacked the statement vehemently. Their objections were all similar. They were amazed that no geneticists or even biologists were on the committee that drew up the statement; they were certain that there was some biological reality to human races; they suspected that races differed in some respects in mental characters; and they were appalled by the invocation of Prince Kropotkin's thesis of hereditary mutual cooperation applied to humans. Among the biologists who objected were L. C. Dunn, Theodosius Dobzhansky, Julian Huxley, H. J. Muller, and Curt Stern; the physical anthropologists were even more vociferously critical of the statement.

Since the whole rationale at UNESCO was to promulgate unassailable science in the fight against racism, the objections of major scientists constituted a severe blow to the credibility of the whole enterprise. Understandably, UNESCO decided to have a second statement, this time to be designed by geneticists and physical anthropologists. Accordingly, UNESCO convened a new committee in 1951 that included geneticists L. C. Dunn (rapporteur), J. B. S. Haldane, A. E. Mourant, and Hans Nachtscheim; Dobzhansky and Huxley contributed to the final wording. Montagu was the only holdover from the earlier committee.

In this statement, human races again existed as judiciously defined biological populations and there was no mention of the inheritance of the cooperative instinct. But the crucial statements were little changed (for the complete UNESCO statement, see appendix 1):

> Available scientific knowledge provides no basis for believing that the groups of mankind differ in their innate capacity for intellectual and emotional development.
>
> There is no evidence that race mixture produces disadvantageous results from a biological point of view.

These statements conveyed the desired impression that biologists thought human races were alike in mentality and that race crossing produced no undesirable biological results; the conclusion was that all races should be treated equally.

But the statements were very carefully worded in the negative. The committee had not actually said that scientists thought there were no hereditary mental differences between races, only that there was no convincing scientific evidence that such differences existed. The committee was perfectly aware that there was also no scientific evidence that races had equal mental capacities. It was a tough problem to find the objective science that led directly to the proper moral conclusion on the race question.

The statement was sent out to 106 prominent geneticists and physical anthropologists for comment before publication (although the published statement was revised very little). Of these, 80 responded; 23 accepted the statement as a whole, including geneticists William Castle, Karl Sax, Jack Shultz, and L. H. Snyder; 26 agreed with the tenor of the statement but disagreed on particulars; and the others disagreed strongly with the statement. German geneticists and physical anthropologists (E. Fischer, F. Lenz, K. F. Saller, W. Scheidt, and H. Weinert) saw the statement as an attempt to combat anti-Semitism with a political statement based upon bad science and were all opposed to it. Greatest criticism was directed to the statement that "available scientific knowledge provides no basis for believing that the groups of mankind differ in their innate capacity for intellectual and emotional development." R. A. Fisher, K. Mather, A. H. Sturtevant, C. D. Darlington, W. Landauer, and H. J. Muller were among the geneticists who objected strongly to this statement. Fisher recommended revising the passage to read: "Available scientific knowledge provides a firm basis for believing that the groups of mankind differ in their innate capacity for intellectual and emotional development, seeing that such groups do differ undoubtedly in a very large number of their genes" (UNESCO 1953, 61).

Muller's comments were more representative of the most of the criticisms:

> I quite agree with the chief intention of the article as a whole, which, I take it, is to bring out the relative unimportance of such genetic mental differences between races as may exist, in contrast to the importance of the mental differences (between individuals as well as between nations) caused by tradition, training and other aspects of environment. However, in view of the admitted existence of some physically expressed hereditary differences of a conspicuous nature, between the averages or the medians of the races, it would be strange if there were not also some hereditary differences affecting the mental characteristics which develop in a given environment, between these averages of medians. At the same time, these mental differences might usually be unimportant in comparison with those between individuals of the same race. (UNESCO, 1953, pp. 48–49)

Muller added that

> it would . . . therefore be unfair for the committee to imply that the passage in question had the approval of geneticists. It happens that your committee has consulted a few geneticists who even though justly eminent, represent a much more extreme point of view on this matter than that prevalent among geneticists in gen-

> eral, or among geneticists who are regarded by their colleagues as having done outstanding work. Moreover, it is difficult for me to believe that most of even that group of geneticists which your committee has already consulted would concur in the particular passage under dispute if they were asked specifically about this point and had also read my protest concerning it. (p. 49)

The available historical evidence indicates that Muller's assessment in 1952 of his colleagues' attitudes about possible hereditary mental differences between races was entirely correct. That is, most of them still believed that races differed in hereditary mental characteristics, but that firm scientific proof was not yet available.

Now came the difficult question for Muller and the others who agreed with his criticisms so far. How were geneticists to use their scientific belief that races probably differed in hereditary mental capacities to conclude that all races should be treated equally in society and that race prejudice should be rooted out of society? Muller did not shrink from the issue:

> It would be a tragic mistake to suppose that the above realistic, scientific view leads to the conclusion that race prejudices are justified. It is highly important, especially at this crisis in the relations between peoples, for the committee to give the correct argument against these prejudices. The essential points are that the different racial groups (a) are enough alike genetically (b) are capable of being so much influenced in mental development by cultural and other environmental factors, and (c) contain such important individual genetic differences for psychological traits within each one of them, that all of them are capable of participating and cooperating fruitfully in modern civilization (as has also been empirically demonstrated). It also follows from this that all men should be given equal opportunities, equal civil rights, and the privilege of being judged and treated entirely as individuals without reference to their racial origin . . . .
>
> Undoubtedly the truth of the point of view above expressed will some time be generally recognized. It would be very unfortunate if in the meantime a statement had been drawn up by the committee which made the argument for fair treatment of one race by another depend upon the spurious notion that they are identical in the genetic basis of psychological traits. (UNESCO, 1953, pp. 50–51)

Now it should be immediately noted that it does not logically follow from Muller's a, b, and c alone that all humans should be given equal opportunities; another deeper, moral assumption is required.

In a personal letter to Dunn, his friend Walter Landauer addressed this issue:

> I fear my philosophy differs in one basic point. I *do* believe that the results of scientific investigation can greatly strengthen ethical judgments arrived at in some other fashion. I do *not* believe that ethical values can ever be derived from scientific data . . . .
>
> The UNESCO document was written on the assumption that from a certain body of scientific facts *necessarily* flowed certain ethical commandments. Perhaps because of this there was, I feel, some yielding to the temptation to treat *terra incognita* as *terra nullius.* It would surely make no difference to the ethical standards of the UNESCO group or to mine if, for instance, an unequal distribution of genes for certain mental traits were demonstrated. The declaration that all men are created equal was a fine one and remains so, even though and in the best sense *because* it is untrue in the biological sphere.

Dunn was much affected by this letter from Landauer and tried but failed to have UNESCO change the basic argument of the statement. He replied to Landauer:

> I agree with you now about the impossibility of deriving ethical judgments from scientific facts . . . in the final text we shall only refer to the inability of any scientific data about race to justify any limitation of the ethical principle of equality. I think you made a telling point

in considering equality a higher principle because untrue biologically.

Indeed, the published versions of both the 1950 and 1951 UNESCO Statements contained a caveat (this one from the second statement): "We wish to emphasize that equality of opportunity and equality under the law in no way depend, as ethical principles, upon the assertion that human beings are in fact equal in endowment." In other words, the committee covered its bases by saying that if the major argument in the statement failed, races still deserved equal treatment in society for moral reasons entirely unrelated to the scientific facts supposedly presented in the statement.

After the statement was published and distributed, Dunn wrote to the official at UNESCO in charge of producing the statement, giving his final assessment as rapporteur. The deepest problem with the whole enterprise, Dunn said, was that "an attempt was made to justify a particular ethical position on scientific grounds." By then, Dunn thought that the ethical position should be based upon moral grounds, with science merely an ally of secondary importance. Such a statement from UNESCO would have entirely undercut their original directive, which was to fight racism by the promulgation of nothing but objective science.

Dunn learned so much from the criticisms of UNESCO's second statement on race that he encouraged UNESCO to publish the criticisms along with the statement; the volume appeared in 1953, much to the credit of Dunn and UNESCO. This 94 page pamphlet is a major document in the development of geneticists' attitudes toward race differences and race crossing (UNESCO, 1953).

Conclusions

By the early 1950s geneticists had reached the following conclusions about race differences and race crossing:

1. Race mixture was biologically harmless. Further major research conducted by Newton Morton and his colleagues on first generation hybrids in Hawaii and a careful review of the literature through the middle 1960s revealed no significant effects of outcrossing upon birth weight, congenital malformation, and stillbirth or infant death (Morton *et al.*, 1967). Before the issue of race differences began to heat up again with the publication of Arthur Jensen's paper in 1969, the question of race crossing, a burning one for geneticists from 1900 through the 1940s, had ceased to be an issue for concern.

2. Most geneticists continued to believe that hereditary mental differences probably existed between human races, but they also, except for a relatively few like C. D. Darlington and R. A. Fisher, believed that scientific evidence for their belief was not conclusive.

3. Geneticists had begun to wrestle substantively with the extremely vexing issue of how to argue for equality in society for all races while holding open the possibility that there might be average differences in intelligence between races. They had not done very well on this issue in the creation of the second UNESCO statement on race.

THE GENETICS SOCIETY OF AMERICA STATEMENT ON HEREDITY, RACE, AND IQ

Twenty years after UNESCO published the deliberations of geneticists on the question of race differences, the Genetics Society of America, the largest and most prestigious society of geneticists in the world, became involved with the same issues.

Much had happened in the ensuing twenty years in the United States to change the cultural millieu in which the deliberations would take place. Among the more influential events were the desegregation decision in the case of Brown *vs.* Board of Education by the U.S. Supreme Court in 1954, the Montgomery bus boycott that signalled new vigor in the civil rights movement, the social unrest of the late 1960s often termed the "black revolution," and strong bids by native Americans, Hispanics, Asians, and other minority groups to take a greater share of the fruits of American culture. There was no time in the history of America when thoughtful citizens were less sympathetic to hereditarian explanations for the differential success of racial groups.

Then in 1969 the Harvard Educational Review published Arthur Jensen's long paper, "How Much Can We Boost IQ and Scholastic Achievement?" His answer was "not much" because most of the variation of IQ in a population he thought was due to heredity. Although his estimate for the heritability of IQ was high, the thesis was hardly new and not intensely controversial beyond the field of educational psychology. But he also added a section applying the same argument to observed differences in IQ between blacks and whites. He concluded that it was a reasonable hypothesis that the IQ differences were caused primarily by genetic differences between the population of blacks and whites, a view he stated rather defensively:

> The fact that a reasonable hypothesis has not been rigorously proved does not mean that it should be summarily dismissed. It only means that we need more appropriate research for putting it to the test. I believe such definitive research is entirely possible but has not yet been done. So all we are left with are various lines of evidence, no one of which is definitive alone, but which, viewed all together, make it a not unreasonable hypothesis that genetic factors are strongly implicated in the average Negro-white intelligence difference. The preponderance of the evidence is, in my opinion, less consistent with a strictly environmental hypothesis than with a genetic hypothesis, which, of course, does not exclude the influence of environment or its interaction with genetic factors. (Jensen, 1969, p. 82)

By the standards of Darwin, Huxley, East, J. B. S. Haldane, Julian Huxley, H. J. Muller, A. H. Sturtevant, and indeed most geneticists who worked before 1953, Jensen's conclusion was less hereditarian than their own views, and not controversial. But this was no longer 1953. In the social realities of 1969, Jensen's conclusion was intensely controversial and it immediately raised a storm of protest. Geneticists, among the first being James F. Crow (1969), Richard C. Lewontin (1970), and Walter F. Bodmer and L. L. Cavalli-Sforza (1970) were involved heavily with the controversy.

The story of the Genetics Society of America "Resolution on Genetics, Race, and IQ" began at the 13th International Congress of Genetics held at Berkeley, California in August 1973. Interest in the issues of heredity, race, and IQ had exploded since the publication of Jensen's 1969 paper. Critics had carefully scrutinized and rejected many of Jensen's arguments, while far fewer supporters like Richard J. Herrnstein, William Schockley, and H. J. Eysenck had defended and expanded the hereditarian viewpoint. Jensen, of course, defended his own views with books, articles, and in public forums. In the same month as the meeting of the International Congress, he sent a notice to his friends and colleagues of three new books on genetics and education. Anti-Jensen feeling ran high in many academic circles and resolutions directed against his work were announced by such organizations as the Eastern Psychological Association, Society for the Psychological Study of Social Issues, American Anthropological Association, American Linguistics Society, and the American Sociological Association.

A small group of scientists and students at the University of California, Berkeley, calling itself the Committee on Genetics and Society (CGS), was strongly opposed to the new hereditarians. After sponsoring a very lively and well-attended informal session on genetics, race, and intelligence at the International Congress, members of CGS decided to distill the basic arguments against Jensen *et al.* into a brief document and resolution for action that they could submit at the Annual Business Meeting of the GSA (held in conjunction with the International Congress). They hoped that members of the GSA would approve their document and resolution and that the society could go on record as opposing the new hereditarians as had many other academic societies.

The document stated that a new revival of hereditarianism had occurred, with some proponents advocating school segregation and sterilization of the "unfit." Such views, the document declared, had in the past led to the excesses of the eugenics movement. Following a brief refutation of the arguments of the new hereditarians came the following three part resolution:

> 1. We consider the conclusions of certain studies on intelligence and heredity, as currently exemplified by the work of Jensen, Herrnstein, Shockley, and Eysenck, to be scientifically invalid.
> 2. We oppose the use of these studies to provide genetic justification for class and racial discrimination.
> 3. We recognize our responsibility as geneticists to become informed about these issues and to speak out in our classes, at our professional societies, and in public arenas against this misuse of genetics.

At the Business Meeting, debate over the document and resolution was intense. Instead of adopting the CGS document and resolution, the membership present voted to appoint an *ad hoc* committee to draft a resolution on genetics, race, and intelligence. The resolution would then be sent to the membership in the form of a ballot, the results to be widely publicized.

The *ad hoc* committee was faced with the same difficult set of issues that earlier faced the geneticists who had drawn up and revised the second UNESCO Statement on Race: how could geneticists, with their unique understanding of the mechanisms of heredity in humans and other organisms, use their expertise to conclude that all racial groups of humans should be treated equally in society? UNESCO had proceeded upon the assumption that the correct science would lead directly to the correct moral conclusion. The basic problem with this approach, as Landauer and Dunn had discovered, was that geneticists seemed forced into advocacy of the view that all races had equal mental capacities in order to conclude that all races should be treated equally in society.

After wrestling with five draft versions over more than a year, the *ad hoc* committee of the GSA produced a version that was sent to the membership in January 1975. Prominently displayed in this document, the only passage printed in capital letters, was the following: "there is NO CONVINCING EVIDENCE OF GENETIC DIFFERENCE IN INTELLIGENCE BETWEEN RACES." Moreover, the final section on the role of geneticists contained this assertion: "It is our duty as geneticists to work to eliminate racial bias in educational opportunity by increasing public understanding of the relations between genetics, race, and intelligence." In other words, geneticists should promote the correct morality by presenting correct science to the public.

The citizen untrained in genetics would probably conclude from the document that geneticists believed a new eugenics movement fired by new hereditarians was upon us and that the new hereditarians were wrong. Geneticists, who ought to know, believed that no hereditary mental differences existed between human races, so all races should be treated equally.

Members of the GSA responded with enthusiasm for the document. Almost 90% of the 1,088 members responding wished to have their names associated with the document. Only 75 members disagreed and most of them were simply against the GSA taking any stand at all rather than disagreeing with the substance of the resolution. But the critiques that did arrive were telling.

The assertion about "no convincing evidence" came in for the most criticism. John A. Moore reflected the opinion of many critics:

> The punch line in the statement is really "there is no convincing evidence of genetic difference between races." If such a statement is read by a geneticist there is little problem but, of course, the statement is meant for a wider audience. For a wider audience, wouldn't it have been more useful—and truthful—to say "there is no convincing evidence of genetic difference between races and neither is there any convincing evidence that all races are equally intelligent." But if we settle for saying that is there any reason to say anything at all?

Only one letter in the entire set of responses addressed the question of the relation of science to morality in the resolution. This came from Norman Horowitz:

> The proposed statement is weak morally, for the following reason: Racists assert that blacks are genetically inferior in I.Q. and therefore need not be treated as equals. The proposed statement disputes the premise of this assertion, but not the logic of the conclusion. It does not perceive that the premise, while it may be mistaken, is not by itself racist; it is the conclusion drawn (wrongly) from it that is racist. Even if the premise were correct, the conclusion would not be justified . . . . Yet the proposed statement directs its main fire at the premise, and by so doing seems to accept the racist logic. It places itself in a morally vulnerable position, for if, at some future time, it is found that the premise is correct, then the whole GSA case collapses, together with its justification for equal opportunity.

Here was Landauer's position all over again.

In 1975 Oliver Smithies of the University of Wisconsin was President of the GSA. He faced a difficult choice. The membership of the GSA had overwhelmingly supported this resolution and its immediate release to the news media; but Smithies also thought some of the criticisms, especially that of Horowitz and those represented by Moore's letter, should be taken into account before the resolution was released. Smithies decided to block the publication of the resolution until he could present the issues to the membership at the next annual meeting of the GSA, scheduled for August 1975. Smithies and some of his colleagues at the University of Wisconsin then drew up a resolution of their own that they hoped the membership would substitute for the one produced by the *ad hoc* committee. Instead, at the meeting the membership rejected both the original *ad hoc* committee version and the new Wisconsin version and directed the *ad hoc* committee to produce a final version, taking into account all of the criticisms.

This version indeed incorporated the criticisms of Horowitz and Moore. It stated (for the complete GSA statement see Appendix 2):

> In our views, there is no convincing evidence as to whether there is or is not an appreciable genetic difference in intelligence between races.
>
> We deplore racism and discrimination, not because of any special expertise but because they are contrary to our respect for each human individual. Whether or not there are significant genetic inequalities in no way alters our ideal of political equality, nor justifies racism or discrimination in any form.

The membership responded even more favorably to this version than to the previous one: 1,488 members responded to the mailing (400 more than before) and 1,390 (94%) wished to have their names associated with the resolultion.

After two and one-half years of intense effort and much controversy, the GSA finally had a resolution on genetics, race, and intelligence that was ready for presentation to the public. Few geneticists, however, seemed terribly proud of the resolution. It was published in *Genetics* in late summer 1976 buried in the supplement, which contains business matters such as the budget, and which is bound separately from the scientific journal that geneticists actually read carefully. So far as I can determine, most members of the GSA never even knew that the resolution was published and certainly no attempt was made to widely publicize the resolution to the news media as originally intended. The only published reference to the resolution that I have ever seen was in a letter to the editor of *Science* in the issue of 7 January 1977. As a document of social significance, the GSA resolution was a failure. Yet as an objective statement of the current scientific understanding of genetics and race, its clear statement of ignorance is accurate. Also, the elevation of the moral principle of equality in society as a more fundamental guide to social policy than any objective scientific data on race differences in intelligence reflects a more sophisticated conception of the complex relationship between science and morality.

Some geneticists in 1976 argued that there was no way to have a resolution that was both politically effective and scientifically accurate. John R. G. Turner (then of the State University of New York and now of the University of Leeds in England), a member of the *ad hoc* committee, wrote that "a scientifically accurate statement on this subject will be politically naive; a politically sound statement will be a scientific weasel. It will be hard to have it both ways."

I do not see why a statement by the most prestigious society of geneticists in the world could not be both politically effective and scientifically accurate. The statement that no one knows whether or not there are average mental differences between races is a clear rebuke to any hereditarians who claim to know that such differences do exist. The assertion that members of the GSA (including many Nobel Prize winners) are committed to the ideal of eliminating discrimination between races, sexes, or social classes and promoting equality of opportunity in society is not politically ineffective just because geneticists are unable to derive this position directly from their scientific knowledge of genetics. Andrei Sakharov did not have to pretend to derive his moral position on human rights from nuclear physics in order to have a significant political impact in the USSR. Nor do the prestigious scientists in Amnesty International feel they must deduce their views on human rights from their scientific expertise in order to be politically effective.

Loehlin, Lindzey, and Spuhler

During the same time that the GSA was debating its resolution on genetics, race, and I.Q., John C. Loehlin, Gardner Lindzey, and J. N. Spuhler were writing their book, *Race Differences in Intelligence,* which appeared in 1975. Prepared under the auspices of the Social Science Research Council's Committee on Biological Bases of Social Behavior and with an advisory board of prestigious scientists, this book was designed to be the objective scientific assessment of the question of race differences and intelligence. The authors embarked on the project in large part because the National Academy of Sciences had rejected the recommendation of one of its subcommittees to prepare an objective analysis of the question.

Their assessment of the evidence from a wide variety of research designs yielded the following conclusion:

> the studies we have reviewed in this chapter provide no unequivocal answer to the question of whether the differences in ability-test performance among U.S. racial-ethnic subpopulations do or do not have a substantial component reflecting genetic differences among the subpopulations. (Loehlin *et al.*, 1975, p. 133)

All the scientific evidence in the book corroborated this conclusion, which I consider to be an objective assessment of the evidence.

Their conclusions about the social and public-policy implications of the *possible* genetic differences between racial-ethnic groups in the U.S. were, however, far less objective.

> We consider it quite likely that *some* genes affecting *some* aspects of intellectual performance differ appreciably in frequency between U.S. racial-ethnic groups—leaving open the issue of which groups, which aspects, and which direction of difference. Thus we consider it most unwise to base public policy on the assumption that no such differences exist. If someone defends racial discrimination on the grounds of genetic differences between the races, it is far more prudent to attack the logic of his argument than to accept the argument and deny any differences. The latter stance can leave one in an extremely awkward position if such a difference is subsequently shown to exist. (p. 240)

The evidence presented in the book does not support the first sentence, although the authors are of course welcome to their speculations. More disturbing is their conclusion that it would be "most unwise to base public policy on the assumption that no such differences exist." As the GSA resolution and the clear conclusions of Loehlin, Lindzey, and Spuhler indicate, there is no way the objective scientific ignorance of hereditary mental differences between races can be the guide to social policy. Here the guide must be moral views derived from the complex cultural web. A person fully cognizant of the current scientific results on race differences might reasonably assume (as a matter of social policy, not science) that no hereditary mental differences exist. Perhaps there would be some social costs; if so, they would probably be vastly less than the terrible social costs of hereditarian assumptions so prevalent in human history thus far.

Loehlin, Lindzey, and Spuhler also argue that some specified further research into hereditary mental differences between human races deserves "fairly high scientific and social priority" (p. 256). Given that all the research on this question up to 1975 left scientists in near total ignorance on the crucial question of hereditary mental differences between races and that the social control necessary to conduct the crucial experiments is deeply unethical in our society, one can understand why many geneticists disagree with the conclusion that further research in this area has a high priority. Bodmer and Cavalli-Sforza conclude:

> Since we believe that, for the present at least, no good case can be made for such studies on either scientific or practical grounds, we do not see any point in particularly encouraging the use of public funds for their support. There are many more useful biological problems for the scientist to attack. (Bodmer and Cavalli-Sforza, 1970, p. 29)

I have no evidence to say what proportions of geneticists now might support the view of Bodmer and Cavalli-Sforza or that of Loehlin, Lindzey, and Spuhler.

FINAL REMARK

Geneticists are generally more qualified than other members of society to assess the scientific evidence of hereditary mental differences between human races. They have made a significant contribution to the controversy by showing clearly how little we actually know about such issues. They are not, however, more qualified than other groups of thoughtful persons to set the social and cultural ideals relating to race relations.

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Appendix 1

UNESCO Statement on the Nature of Race and Race Differences, 1951

Paris, June 1951

The reasons for convening a second meeting of experts to discuss the concept of race were chiefly these:

Race is a question of interest to many different kinds of people, not only to the public at large, but to sociologists, anthropologists and biologists, especially those dealing with problems of genetics. At the first discussion on the problem of race, it was chiefly sociologists who gave their opinions and framed the 'Statement on race'. That statement had a good effect, but it did not carry the authority of just those groups within whose special province fall the biological problems of race, namely the physical anthropologists and geneticists. Secondly, the first statement did not, in all its details, carry conviction of these groups and, because of this, it was not supported by many authorities in these two fields.

In general, the chief conclusions of the first statement were sustained, but with differences in emphasis and with some important deletions.

There was no delay or hesitation or lack of unanimity in reaching the primary conclusion that there were no scientific grounds whatever for the racialist position regarding purity of race and the hierarchy of inferior and superior races to which this leads.

We agreed that all races were mixed and that intraracial variability in most biological characters was as great as, if not greater than, interracial variability.

We agreed that races had reached their present states by the operation of evolutionary factors by which different proportions of similar hereditary elements (genes) had become characteristic of different, partially separated groups. The source of these elements seemed to all of us to be the variability which arises by random mutation, and the isolating factors bringing about racial differentiation by preventing intermingling of groups with different mutations, chiefly geographical for the main groups such as African, European and Asiatic.

Man, we recognized, is distinguished as much by his culture as by his biology, and it was clear to all of us that many of the factors leading to the formation of minor races of men have been cultural. Anything that tends to prevent free exchange of genes amongst groups is a potential race-making factor and these partial barriers may be religious, social and linguistic, as well as geographical.

We were careful to avoid dogmatic definitions of race, since, as a product of evolutionary factors, it is a dynamic rather than a static concept. We were equally careful to avoid saying that, because races were all variable and many of them graded into each other, therefore races did not exist. The physical anthropologists and the man in the street both know that races exist; the former, from the scientifically recognizable and measurable congeries of traits which he uses in classifying the varieties of man; the latter from the immediate evidence of his senses when he sees an African, a European, an Asiatic and an American Indian together.

We had no difficulty in agreeing that no evidence of differences in innate mental ability between different racial groups has been adduced, but that here too intraracial variability is at least as great as interracial variability. We agreed that psychological traits could not be used in classifying races, nor could they serve as parts of racial descriptions.

We were fortunate in having as members of our conference several scientists who had made special studies of the results of intermarriage between members of different races. This meant that our conclusion that race mixture in general did not lead to disadvantageous results was based on actual experience as well as upon study of the literature. Many of our members thought it quite likely that hydridization of different races could lead to biologically advantageous results, although there was insufficient evidence to support any conclusion.

Since race, as a word, has become coloured by its misuse in connexion with national, linguistic and religious differences, and by its deliberate abuse by racialists, we tried to find a new word to express the same meaning of a biologically differentiated group. On this we did not succeed, but agreed to reserve race as the word to be used for anthropological classification of groups showing definite combinations of physical (including physiological) traits in characteristic proportions.

We also tried hard, but again we failed, to reach some general statement about the inborn nature of man with respect to his behaviour toward his fellows. It is obvious that members of a group show co-operative or associative behaviour towards each other, while members of different groups may show aggressive behaviour towards each other and both of these attitudes may occur within the same individual. We recognized that the understanding of the psychological origin of race prejudice was an important problem which called for further study.

Nevertheless, having regard to the limitations of our present knowledge, all of us believed that the biological differences found amongst human racial groups can in no case justify the views of racial inequality which have been based on ignorance and prejudice, and that all of the differences which we know can well be disregarded for all ethical human purposes.

L. C. Dunn (rapporteur), June 1951

1

Scientists are generally agreed that all men living today belong to a single species, *homo sapiens*, and are derived from a common stock, even though there is some dispute as to when and how different human groups diverged from this common stock.

The concept of race is unanimously regarded by anthropologists as a classificatory device providing a zoological frame within which the various groups of mankind may be arranged and by means of which studies of evolutionary processes can be facilitated. In its anthropological sense, the word 'race' should be reserved for groups of mankind possessing well-developed and primarily heritable physical differences from other groups. Many populations can be so classified but, because of the complexity of human history, there are also many populations which cannot easily be fitted into a racial classification.

2

Some of the physical differences between human groups are due to differences in hereditary constitution and some to differences in the environments in which they have been brought up. In most cases, both influences have been at work. The science of genetics suggests that the hereditary differences among populations of a single species are the results of the action of two sets of processes. On the one hand, the genetic composition of isolated populations is constantly but gradually being altered by natural selection and by occasional changes (mutations) in the material particles (genes) which control heredity. Populations are also affected by fortuitous changes in gene frequency and by marriage customs. On the other hand, crossing is constantly breaking down the differentiations so set up. The new mixed populations, in so far as they, in turn, become isolated, are subject to the same processes, and these may lead to further changes. Existing races are merely the result, considered at a particular moment in time, of the total effect of such processes on the human species. The hereditary characters to be used in the classification of human groups, the limits of their variation within these groups, and thus the extent of the classificatory sub-divisions adopted may legitimately differ according to the scientific purpose in view.

3

National, religious, geographical, linguistic and cultural groups do not necessarily coincide with racial groups; and the cultural traits of such groups have no demonstrated connexion with racial traits. Americans are not a race, nor are Frenchmen, nor Germans; nor *ipso facto* is any other national group. Moslems and Jews are no more races than are Roman Catholics and Protestants; nor are people who live in Iceland or Britain or India, or who speak English or any other language, or who are culturally Turkish or Chinese and the like, thereby describable as races. The use of the term 'race' in speaking of such groups may be a serious error, but it is one which is habitually committed.

4

Human races can be, and have been, classified in different ways by different anthropologists. Most of them agree in classifying the greater part of mankind into at least three large units, which may be called major groups (in French *grand-races* in German *Hauptrassen*). Such a classification does not depend on any single physical character, nor does for example, skin colour by itself necessarily distinguish one major group from another. Furthermore, so far as it has been possible to analyse them, the differences in physical structure which distinguish one major group from another give no support to popular notions of any general 'superiority' or 'inferiority' which are sometimes implied in referring to these groups.

Broadly speaking, individuals belonging to different major groups of mankind are distinguishable by virtue of their physical characters, but individual members, or small groups belonging to different races within the same major group are usually not so distinguishable. Even the major groups grade into each other, and the physical traits by which they and the races within them are characterized overlap considerably. With respect to most, if not all, measurable characters, the differences among individuals belonging to the same race are greater than the differences that occur between the observed averages for two or more races within the same major group.

5

Most anthropologists do not include mental characteristics in their classification of human races. Studies within a single race have shown that both innate capacity and environmental opportunity determine the results of tests of intelligence and temperament, though their relative importance is disputed.

When intelligence tests, even non-verbal, are made on a group of non-literate people, their scores are usually lower than those of more civilized people. It has been recorded that different groups of the same race occupying similarly high levels of civilization may yield considerable differences in intelligence tests. When, however, the two groups have been brought up from childhood in similar environments, the differences are usually very slight. Moreover, there is good evidence that, given similar opportunities, the average performance (that is to say, the performance of the individual who is representative because he is surpassed by as many as he surpasses), and the variation round it, do not differ appreciably from one race to another.

Even those psychologists who claim to have found the greatest differences in intelligence between groups of different racial origin and have contended that they are hereditary, always report that some members of the group of inferior performance surpass not merely the lowest ranking member of the superior group but also the average of its members. In any case, it has never been possible to separate members of two groups on the basis of mental capacity, as they can often be separated on a basis of religion, skin colour, hair form or language. It is possible, though not proved, that some types of innate capacity for intellectual and emotional responses are commoner in one human group than in another, but it is certain that, within a single group, innate capacities vary as much as, if not more than, they do between different groups.

The study of the heredity of psychological characteristics is beset with difficulties. We know that certain mental diseases and defects are transmitted from one generation to the next, but we are less familiar with the part played by heredity in the mental life of normal individuals. The normal individual, irrespective of race, is essentially educable. It follows that his intellectual and moral life is largely conditioned by his training and by his physical and social environment.

It often happens that a national group may appear to be characterized by particular psychological attributes. The superficial view would be that this is due to race. Scientifically, however, we realize that any common psychological attribute is more likely to be due to a common historical and social background, and that such attributes may obscure the fact that, within different populations consisting of many human types, one will find approximately the same range of temperament and intelligence.

6

The scientific material available to us at present does not justify the conclusion that inherited genetic differences are a major factor in producing the differences between the cultures and cultural achievements of different peoples or groups. It does indicate, on the contrary, that a major factor in explaining such differences is the cultural experience which each group has undergone.

7

There is no evidence for the existence of so-called 'pure' races. Skeletal remains provide the basis of our limited knowledge about earlier races. In regard to race mixture, the evidence points to the fact that human hybridization has been going on for an indefinite but considerable time. Indeed, one of the processes of race formation and race extinction or absorption is by means of hybridization between races. As there is no reliable evidence that disadvantageous effects are produced thereby, no biological justification exists for prohibiting intermarriage between persons of different races.

8

We now have to consider the bearing of these statements on the problem of human equality. We wish to emphasize that equality of opportunity and equality in law in no way depend, as ethical principles, upon the assertion that human beings are in fact equal in endowment.

9

We have thought it worth while to set out in a formal manner what is at present scientifically established concerning individual and group differences:

(a) In matters of race, the only characteristics which anthropologists have so far been able to use effectively as a basis for classification are physical (anatomical and physiological).

(b) Available scientific knowledge provides no basis for believing that the groups of mankind differ in their innate capacity for intellectual and emotional development.

(c) Some biological differences between human beings within a single race may be as great as, or greater than, the same biological differences between races.

(d) Vast social changes have occurred that have not been connected in any way with changes in racial type. Historical and sociological studies thus support the view that genetic differences are of little significance in determining the social and cultural differences between different groups of men.

(e) There is no evidence that race mixture produces disadvantageous results from a biological point of view. The social results of race mixture, whether for good or ill, can generally be traced to social factors.

Text drafted at Unesco House, Paris, on 8 June 1951 by:

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(From: UNESCO 1953:36–43.)

Appendix 2

Genetics Society of America

Resolution on Genetics, Race, and Intelligence, 1976

Report of the ad hoc *committee*

The bases for intergroup net differences in intelligence quotients are of considerable concern to all citizens, and especially to educators, psychologists, geneticists, and makers of public policy. Geneticists, whose business specifically includes analysis of differences within and between populations, feel a special responsibility to "keep the record straight", and to work to prevent the adoption of unwise public policy based on unwarranted conclusions from inadequate data.

The Genetics Society has grappled with this problem since 1973. We do not feel it is correct to establish an official Genetics Society policy, since "truth cannot be dictated by vote." Instead, an *ad hoc* committee of GSA members, appointed by our 1973 President, Melvin Green, has worked to produce an accurate and reasonable resolution on genetics, race and intelligence, which a large proportion of members can support, and which we hope will be understood and utilized by the general public, including decision makers. The members of this committee, including Harrison Echols, James F. Crow (from September, 1975), Walter E. Nance, David R. Perkins (through August, 1975), Janice B. Spofford, John R. G. Turner, and Elizabeth S. Russell, Chairman, were willing to undertake their task because they felt that in cases where social justice and public policy are concerned, sins of omission may be worse than sins of commission. During the first 16 months of our labor we produced four successive versions of the proposed resolution, involving major input by all committee members, with considerable exchange (by letter and telephone) between members with different outlooks, and with increasing organization, conciseness, and cohesion. Near the end of 1974, President Bruce Wallace asked us to present, as part of the action during his term in office, our fifth version. A letter, including the statement, was sent to members in January 1975 inviting criticism and suggestions, as well as statement of approval or disapproval. Close to one-half (1099) of GSA members responded to this version, and almost 90% of those responding agreed with the substance of each of its four sections. However, eighty-five members also wrote serious letters, many of them challenging, all of them thought-provoking. Some of the letters were wholly supportive, many were generally favorable but suggested specific alterations, and many were sharply critical.

Our 1975 President, Oliver Smithies, was uncomfortable with the idea of publishing a resolution, however generally popular, to which significant objections had been raised. In a July 1975 letter to the membership, he proposed rediscussion of the resolution at the Society's Annual Business Meeting. I refer you to the minutes of that meeting, printed elsewhere in this Records issue of GENETICS, for an account of that lively session. Its net result in regard to the resolution on Genetics, Race and Intelligence was that of the *ad hoc* committee was sent "back to the drawing board" to prepare another version. The committee, assisted by Douglas Futuyma and Sewall Wright, met in Chicago on November 23, 1975, to produce the following resolution:

> PREAMBLE: Recent years have seen a revival of concern about the relative importance of genes and environment in determining differences in intelligence among individuals, social classes, and races. The controversy and the extreme views expressed are not new. The excesses of the early eugenics movement show the pitfalls of naive hereditarian assumptions. Equally unsupportable is the doctrinaire environmentalism that denies any significant role of heredity in important human behavioral traits. Since even well-meant social policies may be harmful if based on error or inadequate knowledge,

we believe that the views of many geneticists should be considered in trying to resolve the current controversy.

STATEMENT OF GSA MEMBERS ON HEREDITY, RACE, AND IQ

Measurement of intelligence:

Because of their reproducibility and widespread use, IQ scores have been the basis for most analyses of genetic and environmental contributions to intelligence. Nevertheless, their limitations as measures of intelligence are widely recognized. Indeed, intelligence has never been defined to the satisfaction of all social scientists. The interpretation of IQ scores is especially troublesome when comparisons are made between different cultural groups. These limitations must be borne in mind in any genetic analysis.

Factors influencing IQ:

IQ scores are attempts to measure the quantitatively varying character of intelligence; such characters are usually influenced by both genetic and environmental factors whose effects and interactions are often difficult to separate unambiguously. Although there is substantial agreement that genetic factors are to some extent responsible for differences in IQ within populations, those who have carefully studied the question disagree on the relative magnitudes of genetic and environmental influences, and on how they interact. Moreover, in general, even if the variation in a trait is largely genetic, this does not mean that the degree of expression of that trait cannot be significantly altered by environmental manipulation. Nor does a large environmental component in variation necessarily imply that we can easily change it.

Racial and class differences in IQ:

It is particularly important to note that a genetic component for IQ score differences *within* a racial group does not necessarily imply the existence of a significant genetic component in IQ differences *between* racial groups; an average difference can be generated solely by differences in their environments. The distributions of IQ scores for populations of whites and of blacks show a great deal of overlap between the races, even in those studies showing differences in average values. Similar although less severe complexities arise in consideration of differences in IQ between social classes. It is quite clear that in our society environments of the rich and the poor and of the whites and the blacks, even where socioeconomic status appears to be similar, are considerably different. In our views, there is no convincing evidence as to whether there is or is not an appreciable genetic difference in intelligence between races.

IMPLICATIONS FOR SOCIETY

All human populations have a vast store of genes in common; yet within populations, individuals differ in genes affecting many characters. Each population contains individuals with abilities far above and below the average of the group. Social policies, including those affecting educational practice, should recognize human diversity by providing the maximum opportunity for all persons to realize their potential, not as members of races or classes but as individuals. We deplore racism and discrimination, not because of any special expertise but because they are contrary to our respect for each human individual. Whether or not there are significant genetic inequalities in no way alters our ideal of political equality, nor justifies racism or discrimination in any form.

THE ROLE OF GENETICISTS

Its our obligation as geneticists to speak out on the state of current knowledge on genetics, race, and intelligence. Although the application of the techniques of quantitative genetics to the analysis of human behavior is fraught with complications and potential biases, well-designed research on the genetic and environmental components of human psychological traits may yield valid and socially useful results, and should not be discouraged. We feel that geneticists can and must also speak out against the misuse of genetics for political purposes, and the drawing of social conclusions from inadequate data.

In January 1976, the GSA membership was polled to determine how many (and which) members wished to have their names associated with this revised resolution. As of April 19, 1976, responses had been received from 1,488, well over half of the total membership (approximately 2,600). Of those responding, 1,390 (94 percent) wished to have their names associated with the resolution. Another 69 would have preferred that members as a whole not take a stand, and 29 specifically did not wish to be associated with this particular statement.

We are, of course, gratified with this strong positive response, and hereby publish this resolution, which we hope is a reasonable, tempered summary of current knowledge (and lack thereof) relating to genetics, race and intelligence, not as an official pronouncement from the Genetics Society of America, but as a statement supported by 1488 geneticists whose signatures are currently on file in my office at the Jackson Laboratory.

Elizabeth S. Russell, *Chairman*
ad hoc Committee
President, Genetics Society of America 1976

(From Genetics 83:S99–S101; July 1976 Supplement.)

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Reflections on the Limits of Science and Technology[1]

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SYNOPSIS. Exuberance over insights gained in the infant field of genetics early this century led scientists to extrapolate beyond their data to heredity of behavioral traits in people. One of the direct consequences was the incarceration of Americans and Canadians of Japanese ancestry during World War II as enemy aliens. Drawing on this personal experience of the misapplication of science, I describe the process of scientific indoctrination and blindness to the limitations of this way of knowing. This led to my attempt to demystify science through the electronic media.

Only recently have I come to understand that two assumptions that impelled me to use television in the first place are wrong. The first was that with access to more information about science, the general public would be in a position of making better informed decisions on issues involving science and technology. The problem is that we are overwhelmed with information and most people lack the ability to distinguish meaningful "signal" (*i.e.*, credible information) from background "noise" (*i.e.*, garbage). We believe in phantoms created by the acceptance of anything because it exists as print or television programs.

My second assumption had been that we need a mechanism to do an in-depth "cost/benefit" analysis of new technologies *before* they are actually made available. But history reveals that the benefits of new technologies are immediate and obvious while the costs are usually hidden and completely unpredictable.

But in the rush to exploit new scientific insights we ignore the fact that science must look at nature in isolated bits and pieces. Knowledge gained in fragments does not yield an understanding of the greater context from which the pieces are taken. With each new discovery, we itch to apply it, forgetting how much we have yet to learn. Our attempts to manipulate nature are often illusions of control created by our ability to overpower nature by brute strength. In the area of genetic engineering, this could be truly disastrous.

I spent three years in a North American concentration camp for the crime of possessing genes that had come to Canada two generations before. I was nine years old when we were released. The incarceration of American and Canadian citizens of Japanese descent was predicated on the notion of the overriding influence of racial heredity in matters of loyalty. General John L. DeWitt who was put in charge of the evacuation and incarceration of Japanese-Americans stated it clearly in his recommendation to the Secretary of War on 14 February 1942:

> ". . . racial affinities are not severed by migration. The Japanese race is an enemy race and while many second and third generation Japanese born on United States soil, possessed of American citizenship, have become "Americanized," the racial strains are undiluted . . . . It, therefore, follows that along the vital Pacific Coast over 112,000 potential enemies, of Japanese extraction, are at large today."

This notion that loyalty and treachery are heritable traits of a distinct race was not the expression of one man's bigotry in a time of stress, the groundwork for it had been laid and nurtured by some of the most reputable biologists and geneticists of the day.

My purpose in this lecture is not to go over the history of biological determinism and eugenics—that has been covered extensively in many books, the most recent one being Daniel J. Kevles' excellent treatise *In the Name of Eugenics.* What I would like to do is to depart from the academic and scientific presentations of the previous speakers and to give you a personal, anecdotal description of my attempt to come to grips with the troubling issue of the relationship between science and society.

The definitive event in my life was the

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[1] From the Symposium on *Science as a Way of Knowing—Genetics* presented at the Annual Meeting of the American Society of Zoologists, 27–30 December 1985, at Baltimore, Maryland.

suspension of all civil liberties of Japanese-Canadians in British Columbia and our eventual incarceration and evacuation to isolated camps in the interior of the province. This was accomplished by the application of the War Measures Act which empowers Parliament to suspend all guarantees ensured by the British North America Act. (In the United States, Executive Order 9066 was signed by President Roosevelt, ordering the roundup of all Japanese-Americans on the West Coast, with the infamous General DeWitt in command of the operation.) The reverberations of that event have pervaded every aspect of the lives of evacuees, not just economically and socially, but psychologically and emotionally. For me, it instilled a lifelong concern for civil rights issues.

After the war, to many Japanese-Canadians, education seemed the main avenue to finding a place in society. I was lucky and did well enough in school to secure a scholarship to Amherst College in Massachusetts. It was there that a genetics course required for all honors biology students captured my heart and mind. As it was taught by Bill Hexter (thanks to his lineage from Curt Stern) the course was a wonderful adventure in ideas. For the first time in my academic career, I could not wait to get to the next class and would sit in lectures entranced at the power and elegance of genetic analysis. I ached to be a part of that great tradition of dedicated, brilliant geneticists and that impelled me through graduate school and postdoctoral work.

GENETICS AND SOCIETY

When I returned to Canada in 1962 as a university faculty member, I had been well trained for the intense, competitive hurly-burly of scientific research. I was driven and drove my students to work long, exciting hours in the lab. Those were the most focussed, intense and satisfying years of my professional career. But I had also begun to teach and in my interactions with undergraduates, we would speculate on the possibility of cloning, improvement of farm animals and crops, genetic engineering in people, and so on. It was those students' penetrating questions in the early '60s that forced me to read up on the history of genetics. And that was the time when the two great passions of my life, genetics and civil rights, converged in a grotesque way. For I discovered eugenics and the role that leading geneticists had played in it early this century.

I learned how scientists, in their exuberance over the powerful insights that the young field of genetics was providing, found it easy to cross the boundary between science and popular predjudice. Words such as "inferior" and "superior" grace their articles in spite of the fact that these are value judgments, not scientifically meaningful adjectives. It was the extrapolation from studies on the inheritance of *physical* traits in other organisms to the heredity of *behavioral* traits in humans that embroiled geneticists in the sad consequences of their optimism. The claimed scientific evidence for inferiority of racial groups and a hereditary basis for many psychiatric disorders led to the enactment of state and federal laws in the U.S.A. restricting immigration from certain countries, prohibition of miscegenation and sterilization of patients in mental institutions.

The ultimate fate of this hereditarian fad was the Nazi program of Race Purification in Germany. We must not forget that German biologists were among the world leaders in genetics. Geneticists cannot escape responsibility for their complicity in the Holocaust by pointing to individuals like Josef Mengele as if he was an aberrant exception. He and his likes were the colleagues and students of an international scientific fraternity that had encouraged and supported them.

My discovery of this sad chapter in the history of genetics has haunted me ever since. I had received a liberal arts education, yet had never encountered the history or philosophy of science. During my education, I never once heard the names of Mengele or prominent geneticists who spearheaded the eugenics movement in the '20s and '30s. Today's science student confronted with the explosion in scientific knowledge has even less time than I did for such courses, while the general public remains almost completely uninformed about the consequences of science and technology (henceforth referred to as S & T). As a scientist then, I have been confronted with the reality that ideas from science can have an explosive impact on society. Yet *my* ignorance of the history of my discipline is amplified many times over in the general public. This effectively disenfranchises the lay public from any input in determining how S & T will be used. As well, I sense the same intoxication with new insights in molecular genetics today that had characterized geneticists earlier in this century. They too, I am sure, had only the best interests of society at heart like today's scientists.

PUBLIC PERCEPTION OF SCIENCE

Even the most cursory inspection of newspaper reports or television news quickly reveals what make up the major preoccupations of the public—they are things economic, political, glamorous and athletic. In spite of regular horoscopes in virtually all papers, few dailies employ full-time science, technology or medical reporters. I have carried out numerous "streeters," person-on-the-street interviews in which people are asked whether S & T affect them in their daily lives. The overwhelming preponderance of people answer "no."

It was this lack of awareness of the general public of the importance of matters scientific to their lives that propelled me into television in 1962. It is strange how people fail to equate the major innovations of this generation—television, satellites, nuclear power, computers, oral contraceptives, xerography, etc.—with science and technology. Initially, this worried me greatly as a scientist, for a society that does not understand science and its value will not support science in a profound way. But as I became more informed about the history of genetics, my concern shifted to the fact that the general public, while deeply affected by S & T, was not in a position to contribute to any meaningful dialogue on how they would be used.

At its most important level, the public's perception of priorities is reflected in the kind of people we elect to political office. In Canada, 80–90% of all members of the federal Parliament come from two professions, law and business. And members of those two professions have been shown to have the least understanding of terms and concepts in S & T. So it's hardly surprising that in the political discourse on the arms race, environmental problems, medical priorities, computers, etc., there is little serious consideration of the technical aspects.

THE POPULAR MEDIA AS EDUCATIVE TOOLS

Television seemed to be a powerful way to educate a large audience about the value, importance and ramifications of scientific research. It had been my assumption that what the public needed were more facts so that they would be able to make more informed decisions about important matters impinging on their lives. That belief has fuelled my career in broadcasting in both radio and television. But over the years, I have come to the conclusion that this assumption was completely wrong. The reason is, for every criterion we wish to apply, we are exposed to more information today than ever before in human history. From percent literacy, to the proportion of university degrees, to hours of television watched, number of books, magazines and papers bought, we have access to unprecedented amounts of information. Some say we have become Infomaniacs.

The problem is that in the popular media, as in most areas of science, there is a massive outpouring of information, the great bulk of which is unimportant, trivial or wrong. The challenge for the public, as it is for scientists, is to distinguish "meaningful signal" from "background noise." But in the popular print and electronic media, background noise is overwhelming. We consume information uncritically, in fragmented bits and pieces, eventually losing sight of where it came from. Take television. I had thought that the programs I was involved with (*Science Magazine, The Nature of Things*) would shine like dazzling gems in a great TV cesspool. Now I should remind you that I grew up before there was any television. My family bought its first TV set long after I had gone to college. So I always assumed that people watch television the way I do—seldom and selectively. So, of course, they would anxiously wait for the week to go by so they could turn on our show when it finally arrived. But that's not the way people watch television at all. The average North American TV set is turned on 7 to 8 hours a day! And the viewer does not spend time intently absorbing the information; we catch snippets that reflect the state of our interest, hunger, bladder, telephone calls, and so on. So we retain nuggets of information snatched from various programs and then all mixed together. One consequence is that I am frequently queried in the streets over items that were, in fact, on *Quincy* or *That's Incredible*. I get credit for an amazing array of reports that are remotely scientific from all kinds of shows!

In numerous encounters with people, I am struck by the number of times I am told of something that is then legitimized by the statement "I read it" or "I saw it on TV." When asked for the specific source, they are seldom able to identify it. In an environment in which the *National Enquirer* and *Omni* are read much more than *Science '85*, *Discovery* or *Scientific American* (you can see what my judgments are on what constitute signal and noise), where *Ripley's Believe It or Not* or *The A Team* are watched by many more than see *Nova* or *The Nature of Things*, the source of "facts" becomes critical. Here I believe the great challenge for science broadcasters is not to provide more information, but insights into the nature of information itself. The great strength of science is the *attitude* of scientists, one of skepticism and a demand for original data so that scientists themselves may assess and decide on the validity of claims. Somehow that has to be put across to the general public as a lesson far more important than chronicling the latest "breakthrough."

COST/BENEFIT ANALYSIS

When I began my career in broadcasting, it was my perception that the basis for a lot of the problems and controversies often accompanying new technologies stemmed from the fact that the two major users of scientific knowledge are the military and private industry. When destructive power and profit are the main priorities determining the application of science, then long-term consequences for the public or the environment seldom weigh heavily in deliberations over whether they will go ahead. I believed that society needed a vehicle for carrying out a cost/benefit analysis of new technologies *before* they were put in place. I assumed that we simply required a more detailed anticipation and prior assessment of all consequences of innovation before it was in place. But now I realize that this is an improbable task.

History informs us that, however beneficent, every technology has a cost. The dilemma we face is that while the benefits of new technology are immediate and obvious, the costs are usually hidden and cannot be predicted *a priori*. So the entire process is heavily loaded against those who might want to hold back (as in the famous debate over recombinant DNA) because they are pressed to provide concrete evidence of deleterious effects. Yet they usually cannot be predicted or anticipated. And so opponents of new technologies appear to be anti-progress neo-Luddites without a legitimate case. Let me give you three examples where costs were simply not predictable beforehand.

HISTORICAL CASE STUDIES

The first concerns DDT. The benefits of DDT were obvious—enormous profits for the chemicals industry and a crude, but powerful method of pest control. And its widespread application did result in millions of lives saved through temporary relief from malaria. But any thoughtful geneticist or ecologist could have argued strongly against the long-term value of DDT on the basis of predictable selection of resistance mutants and enormous disruption in the ecosystem by the nonspecificity of the pesticide. But no amount of prior assessment could have revealed the phenomenon of *biomagnification*, the concentration of molecules up the food chain. Biomagnification was only discovered through the widespread use of DDT. And no one therefore could have predicted that the compound would end up concentrated in the shell glands of birds thereby causing eggs with thinner, breakable shells that would eventually endanger many species.

My second example of our problem concerns the oral contraceptive. Again, the benefits of the pill were obvious, tremendous profits for the pharmaceutical industry and very effective control over fertility. After an extensive field test, the pill was clearly shown to be efficacious with no serious side effects. It was only after *millions* of healthy, normal women had been on the pill for *years* that it was possible to "see" significant detrimental side effects. No amount of careful pretesting could have provided the sample large enough to yield statistically meaningful numbers, so the *kinds* of "costs" incurred by fertility control by synthetic hormones were not predictable.

My final example is the most difficult technology ever produced, nuclear weapons. Here it is worth pointing out that for most of human history, technology always preceded scientific understanding. The atomic bomb was important symbolically because it was the creation of scientists. Some of the greatest intellects of all time in physics, the queen of all sciences, not only conceived the bomb, they sold it and then built it. War has never been the same since and the symbiosis between the military and science has been an uncomfortable reality that few scientists care to acknowledge.

But let me return to the bomb itself. At the time it was successfully built, a strong case was made for dropping it on Japan in the hopes of ending the war quickly and thus avoiding the inevitable blood bath were the Allies to invade the Japanese mainland. (I will not go into the questions of why it had to be dropped on a city, why the second was necessary or whether it would ever have been dropped over Europe.) Again, the potential benefits were clear but I doubt that anyone in 1945 could have anticipated the incredible sophistication and proliferation of nuclear weaponry that we have today. Moreover, no one could have anticipated radioactive fallout—it was first discovered in the Bikini explosion a year later. Years later, it was found that atmospheric explosions punched holes in the ozone layer and also sent an electromagnetic pulse of gamma rays that can knock out electrical connections over a broad area. And now, over 40 years after Hiroshima, we have discovered the phenomenon called *nuclear winter*. It will be very surprising if this is the last "cost" of nuclear weapons to be found. Of course, when we do not know what costs will be, we cannot monitor them and we have to wait for the consequences to appear, often to the detriment of a component in the environment or public health.

So based on history, we reach a devastating conclusion. For most powerful technologies, the costs cannot be anticipated beforehand. Can we continue to buy the obvious benefits of new technologies and remain prepared to bear the costs later when they are finally defined? We have not begun to counter the negative effects of those crude technologies that cause acid rain and toxic pollutants. In a time when micro-electronics, prenatal screening and genetic engineering are exploding ahead, the answer to this question becomes critical.

THE FRAGMENTED VIEW OF SCIENCE

There are many who would argue that what is needed is simply more science and scientific assessment of new technologies before they are used. But here I believe the faith in science itself as a way of knowing is misplaced. For most of humankind's history, we existed within worldviews which were comprehensive explanations of all the cosmic forces impinging on our lives. It was through the possession of worldviews which incorporated all of the accumulated lore and mythology of a culture that there was some sense of control over the immense factors affecting us. Science was a radically different way of describing the world, for it was incapable of providing such comprehensive descriptions of nature. Scientists looked at a part of nature, attempted to isolate it so that factors impinging on it could be controlled and all output measured. In this way, we have gained profound insights into and manipulative power over those isolated fragments of nature. But this is also the weakness of science for it provides us with knowledge in bits and pieces. Most biologists today still operate under the Newtonian belief that the whole can be described and understood as the sum of its parts. Physicists have long abandoned this notion, but to biologists, denial of this faith smacks of the long discredited idea of "Vitalism." Yet physicists know that in spite of all their knowledge of the properties of atomic hydrogen and atomic oxygen, such information is of very little predictive value even for the properties of a molecule of water.

There is a great temptation to seek solutions by focussing on problems at the simplest describable level. Thus, the ongoing dispute over the causes of crime and poverty has always brought strong support for a genetic basis. During a war with Japan, it was easy to use genes governing racial phenotype as a convenient way of picking out prospective traitors. Richard Lewontin once pointed out to me that while everyone carries the bacterium that causes tuberculosis, those who get the disease tend to be socioeconomically deprived. Medical science looks at the cause of TB as the bacterium when, in fact, it is the environmental conditions in which people live. In the same way, the attempt to encapsulate the enormous range and variability of human behaviour and ability through a single number, the IQ score, is an attempt to reduce people to a mere cipher. But this can never encompass the complexity and vastness of personality and behaviour, any more than a description of neural circuitry or base sequences of behavioral genes will.

AN ILLUSION OF CONTROL

It is a dangerous conceit to feel that our ability to read DNA sequences and to synthesize them provides us with understanding and control over the complexities of behaviour and individuality. The apparent power that molecular genetics holds out to us coupled with the tunnel vision of scientists can lead to bizarre "solutions" for social and environmental problems. Already the availability of human growth hormone is leading to the notion that healthy, normal people who happen to be at the short end of the bell curve of height can become candidates for hormone treatment. The current commitment of Western high tech agriculture to large-scale monoculture has made us dependent on a chemical shield against insect and plant pests that is incidentally polluting the air, water and soil. But the pests have been selected so rigidly for resistance that farmers have to turn to ever more powerful and toxic poisons. So now the vaunted powers of biotechnology are being used to engineer resistance into domestic crops to permit even greater use of more toxic substances. This strikes me as a complete misdirection of priorities when we clearly have to kick the chemical habit, not dig ourselves into a deeper addiction.

But as we focus our attention on society's problems, will our "solutions" reflect that inability to see the forest for the trees? Will we solve racism by eliminating race? Will we deal with hazardous factors in the workplace by identifying and removing people with genotypes conferring greater sensitivity to the factors? Will we handle environmental toxics by engineering people to tolerate higher levels of contaminants? Will the ultimate military tool for global skirmishes be weapons with complete ethnic specificity? Unless we confront the limitations of the insights and impact of science and technology in a profound way, we will never gain any hope of controlling this powerful way of knowing.

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Whither Mankind? The Choice Between a Genetic Twilight and a Moral Twilight[1]

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SYNOPSIS. The biological evolution of mankind continues at present, even though for the last few millennia mankind's mode of adaptation has been primarily cultural. The necessary and sufficient conditions for biological evolution are genetic variability and differential reproduction (natural selection). The genetic variation of human populations is immense: no two individuals developed from different eggs can ever be genetically identical to each other. The two components of natural selection—differential mortality and differential fertility—continue unabated in modern mankind. Cultural changes fuel human biological evolution, which may well be faster now than it has ever been.

The genetic endowment of mankind may be deteriorating precisely owing to the advances of modern health care, although this is not occurring as fast as some would have it. The eugenic measures proposed to improve the genetic lot of mankind may be classified into four broad categories: genetic counselling, genetic surgery, germinal selection, and cloning. The first two can be used as measures of negative eugenics, that is, to prevent the spread of harmful gene mutations. The goals of negative eugenics would seem unobjectionable, and so would be their voluntary application; compulsion would violate fundamental human rights. Germinal selection and cloning are primarily proposals for positive eugenics that seek the multiplication of desirable genetic characteristics. Positive eugenic proposals are unacceptable on biological, ethical, and sociopolitical grounds.

INTRODUCTION

The theme of my lecture is provided by two quotations. The first one is from John V. Tunney, U.S. Senator from California.

> "The most important and enduring of our political freedoms are, in my mind, linked with the manner in which the biomedical sciences are understood and applied by our political system."

The second quotation is from the eminent geneticist and humanist, Theodosius Dobzhansky:

> "If we enable the weak and the deformed to live and to propagate their kind we face the prospect of a genetic twilight. But if we let them die or suffer when we can save or help them, we face the certainty of a moral twilight."

These statements are more than one decade old, but they are no less relevant now than when they were written.

The discovery of the evolution of man from nonhuman ancestors is perhaps the most important contribution of the natural sciences to the understanding of human nature. Man knows now that he was not always what he is now, that his biological nature has changed dramatically since the first humans came into existence a few million years ago.

Mankind's biological nature has not only evolved, it is still evolving. There is no basis to the claim sometimes made that the biological evolution of mankind has stopped. The possibility also exists for mankind to direct its own evolution, to introduce human purposes and goals into the process by which human nature changes. Scientific discoveries in the biomedical sciences, particularly genetics and molecular biology, have provided an understanding of ways and means by which the constitution of mankind could be manipulated in an efficient and rapid manner.

I want to discuss here the techniques that have been proposed to control and to direct the biological evolution of mankind. I will first enumerate the biological methods proposed; second, I shall consider whether these methods *can* be used, that is, whether the required biological know-how is indeed presently available; finally, I will raise the question whether the proposed methods *should* be used: numerous and difficult ethical, legal, religious, and socio-political issues are at stake. Before entering these matters, I shall briefly review the evidence showing that modern mankind continues to evolve biologically.

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BIOLOGICAL EVOLUTION AND CULTURAL EVOLUTION

Mankind is engaged simultaneously in two kinds of evolutionary development, the biological and the cultural. Human evolution can be understood only as a result of the interaction of these two developments. They correspond to the two kinds of heredity existing in man, the genetic and the cultural, which may be called the *endosomatic* and *exosomatic* systems of heredity. Genetic inheritance in man is very much like that of any other outbreeding sexually reproducing species; it is based on transmission of genetic information encoded in the DNA from one generation to the next, via the sex cells.

In addition to his biological system of inheritance, man passes on to other members of the species a cultural inheritance. Cultural inheritance is based on transmission of information by a teaching-learning process, which is, in principle, independent of biological parentage. Culture, in the sense I use it here, is a very inclusive concept; it is the sum total of habits, ways of life, techniques of doing things, language, religious and ethical traditions, science, art and technology; it includes, in general, all that people know or do as a result of having so learned from other human beings. Culture is acquired by every person from parents, relatives and neighbors and from the whole human environment, through imitation and direct communication, and through books, newspapers and radio, television and motion pictures, and by any other means of communication.

Because of his cultural inheritance man can accomplish something impossible to any other organism, he can transmit experience cumulatively down the generations and incorporate its results directly into the evolutionary system. A favorable genetic mutation newly arising in an individual can be transmitted to a sizable part of the human population only through innumerable generations. A new scientific discovery or technical achievement of the human mind can be transmitted to the whole of mankind, potentially at least, in a single generation. Cultural evolution is specifically human and provides man with a power of adaptation to the environment not available for other organisms. Ortega y Gasset, the Spanish philosopher, said that the greatest advantage of man over the animals is that humans are invested with what he called a "social memory," besides the individual memory that they share with other animals.

Adaptation of a living species to its environment is the chief agency promoting and directing biological evolution. Adaptation takes place through natural selection which results from the differential survival and reproduction of the genetic variants present in the species. In mankind, however, and in mankind alone, adaptation can take place also by cultural change. In fact, culture is an instrument of adaptation considerably more efficient than the biological mechanisms. It is more efficient because it is more rapid and because it can be directed. The efficiency of cultural adaptation can easily be evidenced. In fact, for the last few millennia man has been adapting his environments to his genes more often than his genes to his environments.

In order to extend its geographical habitat a population must become adapted, through slow accumulations of genetic mutations sorted out by natural selection, to the climatic conditions, different sources of nutrition, different competitors, etc., existing in the geographic area to be colonized. The discovery of fire, and the use of clothing and shelter, allowed man to spread over the whole earth, except for the frozen wastes of Antarctica, without the anatomical development of protective fur or hair. Man did not wait for genetic mutants promoting wing development; he has conquered the air in a somewhat more efficient and versatile way by building flying machines. Mankind travels through rivers and seas without gills or fins. The exploration of outer space does not require mutations providing some humans with the ability to breathe with low oxygen pressures or adapted to conditions of weightlessness. Astronauts carry their own oxygen and specially equipped pressure suits. Man has replenished the earth and is on his way to conquer outer space not by adaptation of his genes to the new environments, but by modifying the environments according to the needs of his genes. It was the appearance of culture, a superorganic form of adaptation, that made mankind the most successful living species. From obscure beginnings in Africa mankind has become the most abundant species of mammal on earth. Numbers may not be an unmixed blessing, but they are one of the measures of biological success.

Nevertheless, the superorganic has not annulled the organic: biological evolution continues in mankind, and it may be taking place at a faster pace than ever precisely because it is fueled by cultural evolution. Cultural and biological evolution are mutually interrelated. The existence and development of human culture are possible only so long as the genetic basis of human culture is maintained or improved; there can be no culture without human genotypes. At the same time, cultural evolution is the most important source of environmental change promoting the biological evolution of man.

BIOLOGICAL EVOLUTION IN MODERN MANKIND

There is no basis to the claim that the biological evolution of mankind has stopped. That mankind continues to evolve biologically can be shown because the necessary and sufficient conditions for biological evolution persist. These conditions are genetic variability and differential reproduction (natural selection). There is an immense wealth of genetic variation in mankind. Recent biochemical studies have shown that, on the average, a person is heterozygous at least at 6.7 percent of its genes. If we assume that the human genotype consists of 30,000 pairs of genes (which may be an underestimate), a person would be heterozygous at more than 2,000 genes. Such person can potentially produce more than $2^{2,000} \cong 10^{600}$ different kinds of sex cells. Even if we assume that the number of pairs of genes in man is only 10,000 (certainly an underestimate), the number of different kinds of sex cells that can be potentially produced by a person would be 10^{200}, a number immensely large: the number of atoms in the universe is about 10^{75}, a very small number by comparison. It follows that, with the trivial exception of twins developed from a single fertilized egg, no two people who live now, lived in the past, or will live in the future, are likely to be genetically identical. Such is the biological basis of human individuality.

Does natural selection continue to occur in modern mankind? Natural selection is simply differential reproduction of alternative genetic variants. Therefore, natural selection will occur in mankind if the carriers of some genetic constitutions are likely to leave more descendants than the carriers of other genotypes. It might seem that due to the progress of medicine, hygiene, and nutrition most people now survive beyond reproductive age, and thus that natural selection is hardly or not at all operating in modern mankind. But this inference is based on a misconception. Natural selection consists of two main components: differential mortality and differential fertility; both persist in modern mankind.

Death may occur between conception and birth (prenatal) or after birth (postnatal). The proportion of prenatal deaths is not well known (death during the early weeks of embryonic development may be totally undetected), but it is known to be substantial. Such deaths are often due to deleterious genetic constitutions, and thus they have a beneficial selective effect in the population. The intensity of this form of selection has not changed much in the recent past, although it has been slightly reduced with respect to a few genes such as those involved in blood-group incompatibilities.

Postnatal mortality has been considerably reduced in recent times, particularly in technologically advanced countries. For example, in the United States somewhat less than 50 percent of those born in 1840 survived to age 45, whereas it is estimated

TABLE 1. *Percent of Caucasian Americans born between 1840 and 1960 surviving to age 15 and to age 45.**

	Surviving to age 15		Surviving to age 45	
Birth	Men	Women	Men	Women
1840	62.8	66.4	48.2	49.4
1880	71.5	73.1	58.3	61.1
1920	87.6	89.8	79.8	85.8
1960	96.6	97.5	92.9	95.9

* The values for 1960 are projections. (After Kirk, 1968)

that more than 90 percent of those born in 1960 will survive to that age (Table 1). In other regions of the world postnatal mortality remains quite high although there also it has generally decreased in recent decades. Postnatal mortality, particularly where it has been considerably reduced, is largely due to genetic defects, and thus it has a favorable selective effect in human populations. More than 2,000 genetic variants are known that cause diseases and malformations in humans; such variants are kept at low frequencies due to natural selection.

It might seem at first that selection due to differential fertility has been considerably reduced as a consequence of the reduction in the average number of children per family taking place in many parts of the world during recent decades. However, this is not necessarily so. The intensity of fertility selection depends not on the *mean* number of children, but on the *variance* in the number of children. It is clear why this should be so. Assume that all people of reproductive age marry and that all have exactly the same number of children; then, there would not be fertility selection independent of whether couples had all very few or all very many children. Assume, on the other hand, that the mean number of children per family is low, but some families have no children at all while others have many; then, there would be considerable opportunity for selection—the genotypes of parents producing many children would increase in frequency at the expense of those having few or none. Studies of human populations have shown that the opportunity for natural selection often increases as the mean number of children decreases (Table 2). There is no evidence that natural selection due to fertility has decreased in modern human populations.

TABLE 2. *Mean number of children per family and opportunity for fertility selection in various human populations.*

Human population	Mean number of children	I_f*
Rural Quebec, Canada	9.9	0.20
Gold Coast, Africa	6.5	0.23
New South Wales, Australia (1898–1902)	6.2	0.42
United States, women born in 1839	5.5	0.23
United States, women born in 1871–1875	3.5	0.71
United States, women born in 1928	2.8	0.45
United States, women born in 1909	2.1	0.88
United States, Navajo Indians	2.1	1.57

* I_f is the "index of opportunity for selection due to fertility," which is calculated as the variance divided by the square of the mean number of children. The opportunity for selection usually increases as the mean number of children decreases. (After Crow, 1958)

It may be that natural selection will decrease in intensity in the future, but it will not disappear altogether. So long as there is genetic variation and the carriers of some genotypes are more likely to reproduce than others, natural selection will continue operating in human populations. Cultural changes, such as the development of agriculture, migration from the country to the cities and from country to country, environmental pollution, and many others, create new selective pressures. The pressures of city life, for example, are partly responsible for the high incidence of mental disorders in certain human societies. Human environments are changing faster than ever owing precisely to the accelerating rate of cultural change; and environmental changes create new selective pressures thereby fueling biological evolution.

THE BIOLOGICAL FUTURE OF MANKIND

Where is human evolution going? Biological evolution is directed by natural selection, which is not a benevolent force guiding evolution toward sure success. Natural selection is a process bringing about genetic changes that often appear purposeful because they are dictated by the requirements of the environment. The end result may, nevertheless, be extinction—more than 99.9 percent of all species which ever existed have become extinct. Natural selection has no purpose; man alone has purposes and he alone may introduce them into his evolution. No species before mankind could select its evolutionary destiny; mankind possesses techniques to do so, and more powerful techniques for directed genetic change are becoming available. Because we are self-aware, we cannot refrain from asking what lies ahead, and because we are ethical beings we must choose between alternative courses of action, some of which may appear as good, others as bad.

The argument has been advanced that the biological endowment of mankind is rapidly deteriorating owing precisely to the improving conditions of life and to the increasing power of modern medicine. The detailed arguments that support this contention involve some mathematical exercises, but their essence can be simply presented. Genetic changes (*i.e.*, point or chromosome mutations) arise spontaneously in humans as well as in other living species. The great majority of newly arising mutations are harmful to their carriers. In a human population under the so-called "natural" conditions, that is, without the intervention of modern medicine and technology, the newly arising harmful mutations are eliminated from the population more or less rapidly depending upon how harmful they are. The more harmful the effect of a mutation, the more rapidly it will be eliminated from the population by the process of natural selection. However, owing to medical intervention, the elimination of some harmful mutations from the population is no longer taking place as rapidly and effectively as it did in the past.

Let us consider an example. Retinoblastoma is a cancerous disease attributed to a dominant mutation. The unfortunate child with this condition develops during infancy a tumorous growth which starts in one eye, and rapidly extends to the other eye and then to the brain causing death before puberty. Surgical treatment makes it now possible to save the life of the child if the condition is detected sufficiently early, although usually one eye at least is lost. The treated person can live a more or less normal life, marry, and procreate. However, if the genetic determination is due, as it is thought, to a dominant gene, one half of his progeny will, on the average, be born with the same genetic condition and will have to be treated. Before modern medicine, every mutation for retinoblastoma arising in the human population was eliminated from the population in the same generation owing to the death of its carrier. With surgical treatment, the mutant gene can be preserved and new mutations arising each generation are added to those arisen in the past.

There are many deleterious hereditary conditions, the manifestations of which can now be totally or partially cured, and their number is increasing. Another well known example is phenylketonuria (PKU), requiring a very careful diet to prevent its devastating effects on the mental and physical health of its carriers. The carriers of these hereditary diseases now survive and may produce offspring, thus transmitting the deleterious genes to the following generations. The more hereditary diseases and defects are cured today, the more of them will be there to be cured in the succeeding generations.

It must be pointed out that the proportion of individuals affected by any one serious hereditary infirmity is relatively small. For instance, about two out of every 100,000 newborn children will suffer from retinoblastoma; and this is a typical figure for hereditary conditions, such as PKU, causing death of their carriers before adulthood. There are, however, many such hereditary ailments, which on the aggregate make the problem very serious. The more than two thousand known serious physical infirmities determined by genes include metabolic disorders like phenylketonuria; defects of the skin, the skeleton, the blood and vascular systems; defects of the eye (like retinoblastoma), ear, or nervous system; diseases of the muscular system (like muscular dystrophy, which affects about one out of every thousand persons in the United States), and so on. When all these hereditary ailments are considered together, the proportion of persons born who will suffer from a serious handicap during their lifetimes owing to their heredity is more than two percent of the total population. Some 70 million children are born in the world each year; about one million and a half of them carry hereditary conditions determining serious handicaps to their physical well-being.

The problem becomes more serious when mental defects are taken into consideration. More than two percent of the population are affected by schizophrenia or a related condition known as schizoid disease, ailments which may be in some cases determined by a single mutant gene. Another three percent or so of the population suffer from mild mental retardation (IQ below 70), a condition largely determined polygenetically, that is, by the interaction of multiple genes. More than 100 million people in the world suffer from mental impairments due in good part to the genetic endowment they inherited from their parents.

THE PROMISE OF EUGENICS

Temperamentally, I am not a prophet of doom, but problems are not solved by ignoring them. The incidence of severe hereditary ailments is not increasing as rapidly as some have claimed. The number of genetically determined conditions that can be cured at present is not yet very large. But every day we are learning to cure new ones, and each cure contributes to the further genetic deterioration of mankind. Is it possible to stop, or to reverse, this process? Can we improve the hereditary endowment of mankind?

Eugenics is the science and practice seeking to improve the genetic endowment of mankind. Two kinds of eugenics may be distinguished: positive and negative. *Negative eugenics* is concerned with avoiding the spread of harmful genes, while *positive eugenics* seeks the multiplication *in toto* or in part of the genotypes of individuals with particular desirable traits. Eugenics is a matter fraught with sociopolitical and ethical implications; I shall have to deal with such implications and will thus be moving out of scientific ground.

Methods proposed to improve the genetic endowment of mankind may be classified into four broad categories: the first two are primarily methods of negative eugenics, the other two of positive eugenics.

1. *Genetic counselling* is a practice which is becoming increasingly common in the United States and other countries. Prospective parents are informed about the genetic nature of a given condition, which may be known to exist in one of them or in their families, and about the chances of its transmission to their offspring. So advised, the prospective parents may choose not to have a child, or may take their chances on a normal child. Genetic counselling can be supplemented with amniocentesis: a sample of the amniotic fluid surrounding the fetus inside the mother's womb is obtained and examined for chromosomal and other genetic abnormalities. The prospective mother can be informed whether or not the fetus carries a certain genetic defect, and she may choose to have an abortion if such is the case.

The body politic could pursue a genetic program based on genetic counselling, amniocentesis and abortion. Persuasion could be supplemented with financial incentives, sterilization, and other coercive measures in order to restrict carriers of unwanted genetic traits from procreating.

2. *Genetic surgery*, also called "genetic engineering" and "genetic therapy," refers to the direct manipulation of the genetic material. Consider, for example, sickle-cell anemia, a condition caused by the substitution of a single nucleotide in the gene coding for the beta chain of hemoglobin; the abnormal nucleotide could be replaced by the normal one, or the whole defective gene (or segment thereof containing the abnormal nucleotide) could be replaced by a normal one. The recently developed recombinant DNA techniques would be the methods to achieve the desired genetic changes.

3. *Germinal selection* is a technique ardently proposed by the eminent geneti-

cist and Nobel laureate, M. J. Muller (1890–1967). The technique involves the extensive use of sperm and egg cells from individuals with desirable genetic constitutions through artificial fertilization; the frequency of the genetic variants possessed by such individuals would greatly increase in the population.

Muller's plan begins with the establishment of sperm banks for storing the seminal fluid of men of great achievement; this semen could be made available to any woman who would prefer to have a child fathered by a great man rather than by her husband or lover. Through artificial insemination, millions of women could be fertilized with the seminal fluid of a few eminent men. According to Muller, few women would refuse to have a child fathered by men the like of, say, Leonardo da Vinci, Lincoln, Beethoven or Einstein.

But Muller suggests going further: women produce some 500 eggs each through their lifetime; they can have only a few children because of the long nine-month pregnancies. Women of great excellence could be selected, their eggs flushed out and preserved under physiological conditions until requested by a prospective mother. A married couple could then select the genetic mother as well as the genetic father of their child: eggs fertilized in a test tube would be implanted in the prospective mother and allowed there to develop in the old-fashioned way. With further technological progress, the artificially fertilized egg could develop in a clinic outside any woman's womb, and hence independently of individual choice.

4. *Cloning* (or "twinning") proposes the multiplication of the complete genotype of particular individuals. Cloning of the full genotype of an individual has been practiced with some success in frogs and toads. An unfertilized egg obtained from a female is emptied of its *nucleus*, which contains the hereditary information. The nucleus of a cell from the body of a donor individual is extracted and implanted in the pre-emptied egg. The egg is then induced to develop; the resulting organism is genetically identical to the donor of the nucleus. In the case of humans, the development of the egg could occur in the womb of foster mothers or in properly developed incubators. Cloning could produce an unlimited number of people genetically as similar to each other and to the donor as identical twins are. The genetic constitution of a chosen man or woman, say a rock star, a great politician, or an eminent scientist could be multiplied at will. Conceivably, a new mankind could be obtained consisting of only a few human types, each one existing in millions, or hundreds of millions of genetically identical copies.

STATE OF THE ART

One or several of these Brave New World proposals have been advanced as the means to improve the genetic lot of mankind. It may be worthwhile to examine briefly the "state of the art," that is, up to what extent the appropriate technical know-how exists, or is likely to exist in the near future.

There is little doubt that the first category of techniques could be used at present. People can be encouraged, discouraged, or restrained from reproducing. Sterilization is a rather simple process and is voluntarily performed throughout the world in thousands of individuals every year. Amniocentesis is a delicate technique which is nevertheless practiced every day without serious risks in many hospitals in the U.S. and elsewhere.

The technology of recombinant DNA is only a few years old and is developing at an increasing pace. Insertion and deletion of genes and gene segments is practiced with some success in microorganisms, in insects such as *Drosophila* flies, and in human cells cultured in the laboratory. There remain problems with the specificity of the genetic changes accomplished and with the degree of success (only a fraction of the organisms or cells targeted become transformed). Recombinant DNA techniques could be used to correct a defective gene in the cells of the body where the gene's function is essential; for example, the sickle-cell gene could be replaced in the bone marrow cells from which the red blood cells and hemoglobin derive. Success would in this case cure the individual but would have no genetic consequences for the population. If the defective gene were successfully corrected in the germ cells the change would have eugenic consequences. It seems likely that germinal correction of human genes will be possible with the necessary degree of success within the next decade or two.

The preservation of human semen under physiological conditions for long periods of time is feasible. Commercial sperm banks are now in existence: more than a dozen throughout the world. Several thousand cases of successful artificial insemination are estimated to occur per year in the United States alone; several hundred documented normal births have resulted from the use of semen obtained from sperm banks. A few of them came from semen obtained from a California sperm bank where only Nobel Prize laureates and other distinguished men can be donors. Artificial insemination is often used by couples when the husband is infertile rather than for eugenic reasons, but eugenic goals are not necessarily precluded. There are not yet commercial banks for the storage of women's eggs.

Artificial fertilization of human eggs in the test tube has been repeatedly performed during the last few years in several laboratories in various countries. No human embryo has been fully developed outside a woman's womb. In all reported cases of test-tube fertilization of human eggs, the embryos either died spontaneously, or were intentionally destroyed after only a few weeks of development, or were reimplanted in a woman's womb and there allowed to develop. There are well authenticated cases of an egg fertilized in the test tube that was implanted in a woman's uterus and eventually resulted in a normal and healthy individual. It seems that the technology required for the artificial development of a human embryo fully outside a woman's womb could become available in the near future if sufficient economic and scientific effort were dedicated to obtain it. But this, in any case, is not necessary in order to achieve some of the eugenic goals.

The techniques of somatic twinning or cloning have been successfully employed with frogs and other lower vertebrates. Several laboratories in the world are at present working on the application of similar techniques to mice, guinea pigs, rats, and other mammals. We cannot, of course, tell whether they will eventually be successful. But if cloning techniques are developed for other mammals, their application to man will only be one step removed. The embryological development of mice, rats and guinea pigs is basically similar to that of a human being.

BETWEEN UTOPIA AND HADES

The ethical and sociopolitical implications of eugenics are enormous. Not all the methods mentioned above can presently be used as eugenic measures, but some could and others will become available in the future. I now raise the question whether such methods should or should not be applied to human populations. In so doing I leave the grounds of scientific discourse and enter the fields of ethics, sociology, and politics. The issues at stake are very complex. Among the many distinctions which bias these issues are whether the measures are to be applied only to individual cases as determined by experts, or whether they will become available to the public at large.

I shall now briefly state my opinion about what eugenic measures could, and perhaps should, be applied to man, and which ones should be avoided. I fully subscribe to the conviction expressed by John V. Tunney, when he was U.S. Senator from California, that we must begin right now the debate about the eugenic issues raised by progress in the biomedical sciences. As Tunney says, "The techniques must be discussed and debated among lawyers, doctors, theologians, legislators, scientists, journalists and all other segments of society. The issues raised require interdisciplinary attention." In the formulation of the following observations, psychological, sociological, ethical and religious considerations are of paramount importance. I shall thus be treading outside my field of professional competence. However, if we are to begin the dialogue proposed by Tunney, I believe that to express my opinions is not only justified, but indeed required, even though they will unavoidably reflect value judgements.

Negative eugenics seeks to prevent the spread of undesirable genetic traits by using the techniques in the first two categories: genetic counselling (including either advice or coercion against the reproduction of individuals with the genetic defects) and genetic surgery.

Genetic counselling is desirable, because it prepares prospective parents to make informed choices. I believe that parents should be advised not to have natural children whenever these have a high probability of having a very serious genetically determined defect—for example when a prospective parent has been cured of a dominant lethal condition, such as retinoblastoma, and has, therefore, a one-half probability of a defective child; or when both parents are heterozygous for the same recessive lethal gene, in which case there is a one-quarter probability of having a child homozygous for the deleterious gene. Moreover, I believe that amniocentesis should be made available to parents, at least when the genetic risks are high. I also believe that abortion is morally and socially preferable to bringing into the world a severely handicapped child, such as an individual with Down's syndrome, although I realize that many people may disagree with me for religious or other reasons.

I maintain that, in general, known carriers of a severely deleterious dominant gene should be discouraged from reproducing, even when the gene is not lethal, although the lesser the deleterious effects of the gene the smaller is the moral and social obligation of the carriers not to have children. However, there are factors, personal and otherwise, beyond the genetic considerations advanced here, that qualify the degree of moral responsibility of prospective parents in particular cases. An extensive treatment of the matter is not my goal, but only to raise the issues and to illustrate the problems and kinds of possible solutions by dealing with simple cases.

Governments could make it compulsory for people to follow the advice of genetic counsellors. As a general policy this would be a flagrant violation of human rights, and thus I strongly oppose it. It should be further noted that as a method to improve the genetic endowment of human populations, compulsory genetic counselling is inefficient, particularly because its effects on changing genetic frequencies are extremely slow. My own views on this matter are motivated more by the desire to reduce individual human misery than by the hope of eugenic success.

The use of genetic surgery to correct serious genetic defects appears to me ethically and socially unobjectionable. A person choosing to have a genetic defect corrected is making a decision as unobjectionable as a person who willingly chooses to have corrective surgery (such as the removal of a diseased kidney). Genetic surgery would be socially commendable if the defective gene were also corrected in the germinal cells of a person, because it would then benefit the progeny as well as the individual. The difficulty with genetic surgery is that, as previously noted, appropriate techniques usefully applicable to human beings do not yet exist.

Positive eugenics seeks to improve the genetic endowment of mankind through the multiplication of desirable genetic constitutions. The appropriate techniques belong in the third and fourth categories listed above: selecting the sperm or eggs of gifted individuals and multiplying their genotypes by twinning.

The first point to make concerning the techniques of germinal selection and cloning is that the advocates of such Brave New World proposals generally ignore a fundamental genetics notion, namely that the phenotype of an individual is not determined exclusively by its genotype, but results from the interaction between the genotype and the environment. This is true of all organisms, but is most significant in the case of human beings because of the plasticity of their behavior and the decisive influence of the cultural components of the environment. The genotype does not determine the phenotype of an individual but only its "range of reaction." In different environments the same genotype may produce very different individuals. Thus the genotype of a great benefactor of mankind, of a great national leader, of a great scientist, or of a saint, might in a different set of environmental circumstances develop into a tyrant, a criminal, or a bum. This point has been cogently made by the Nobel Laureate geneticist George W. Beadle: "Few of us would have advocated preferential multiplication of Hitler's genes. Yet who can say that in a different cultural context Hitler might not have been one of the truly great leaders of men, or that Einstein might not have been a political villain." In order to obtain another Einstein from Einstein's genotype, we would have to provide the latecomer with exactly the same environment and education, the same challenges and experiences, the same parents, teachers, and friends as those of the original Einstein. This is an impossibility. Thus trying to multiply the Einsteins, the Lincolns, and the Gandhis, we might obtain instead Stalins, Hitlers and Rasputins.

Positive eugenic measures raise fundamental sociopolitical issues that I do not think can be satisfactorily resolved within a democratic society dedicated to the protection of civil liberties: Which one is the ideal genotype? What are the characteristics that should be multiplied? Who makes such decisions? Frequently, high intelligence is identified as a desirable characteristic, but artistic ability and a host of emotional and moral qualities are at least as important. John V. Tunney has asked: "How can we compare intelligence (even assuming it can be defined) with love?" I believe that few of the major problems facing the nations of this world could be solved with increased intellectual acuity, while much progress could be made if the individual and social morals were enhanced.

I believe that there is no way in which wise choices can be made as to the genetic characteristics to be multiplied, nor do I see how such decisions could be satisfactorily reached within the framework of a democratic society. But let us assume for a moment that agreement can be obtained about which individuals possess genetic characteristics to be multiplied. There are reasons to doubt that germinal selection would have significant overall favorable genetic effects on mankind for the following reasons among others:

(1) As pointed out, the genotype does not unambiguously determine the phenotype.

(2) The fitness of a genotype is determined by complex interactions between genes at different loci, but genetic recombination would occur in the formation of the sex cells of the selected individuals with unpredictable results, and the genomes received from the two genetic parents might not favorably interact.

(3) Exclusive use of semen from a few men or of eggs from a few women would reduce the genetic diversity of mankind, a decidedly undesirable prospect.

(4) It seems unlikely that a large fraction of women would choose to be fertilized with the semen of distinguished men rather than by their husbands; it sems even more unlikely that many women would choose to act as incubators for embryos altogether derived from other people's gametes if they can have their own children.

As a means to change the genetic constitution of mankind, cloning the genotypes of chosen individuals would be more effective than any other technique. The production of even a single individual by cloning seems to me ethically repugnant; extensive human cloning would endanger the very survival of a democratic society.

I believe that study groups consisting of biologists, physicians, sociologists, philosophers, legislators, and political and religious leaders should investigate this matter and provide advice and guidance to governments so that human cloning never comes to pass. These study groups should also be concerned with the other eugenic proposals and their present or future application. Cooperation beyond national boundaries will be necessary; the future welfare, and even the survival, of mankind are at stake. The Kingdom as well as the Darkness lie ahead. We must make sure while trying to follow the road to Utopia that we do not take the road to Hades.

ACKNOWLEDGMENTS

This lecture was delivered in Baltimore, on 28 December 1985 as part of the Symposium on "Science as a Way of Knowing.

III, Genetics," organized by Professor John A. Moore. I want to express my appreciation for his invitation and more for his efforts on behalf of science teaching and the survival of rationality in the United States, of which efforts the organization so far of three symposia on Science as a Way of Knowing is only one important instance. I have presented variations of the same lecture at the University of North Carolina, Chapel Hill, on 5 December 1985, as the "Helen P. Mangelsdorf Distinguished Lecturer," and at the California State University, Long Beach, on 24 February 1986, as the "ARCO Visiting Speaker." The comments received from the audience on all three occasions have been helpful in the preparation of the final text.

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The quotations from U.S. Senator John V. Tunney are from the Congressional Record, Vol. 118, No. 83, 23 May 1972. Other references are:

Crow, D. F. 1958. Some possibilities for measuring selection intensities in man. Human Biology 30: 1–13.

Dobzhansky, Th. 1973. *Genetic diversity and human equality.* Basic Books, New York.

Kirk, D. 1968. Patterns of survival and reproduction in the United States: Implications for selection. Proc. Natl. Acad. Sci. U.S.A. 59:662–670.

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Films and Videotapes in Genetics[1]

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There are many films and/or videotapes available for classroom and laboratory use in the teaching of genetics. There follows a list of 16 mm films and videotapes which, based on title and description from film catalogues, would appear useful in the instruction of various aspects of genetics. To further assist in evaluating the effectiveness of these films and videotapes, contact the distributor and request to speak with a media resources specialist familiar with their content. Most of the films and videotapes listed by title below are readily available for rental from major university film libraries. We have, therefore, included a listing of the major university film libraries in the United States. This list was taken from *Educational Film Locator of the Consortium of University Film Centers and R. R. Bowker Company* (2nd ed., 1980, R. R. Bowker, 1180 Avenue of the Americas, New York, New York 10036). The Bowker publication is extremely useful and provides information on rental policy, fees, booking period, etc. NICEM (University of Southern California, University Park, Los Angeles, California 90007) is another helpful source of audiovisual information. It publishes an *Index to 16 mm Educational Films* (8th ed., 1984) and *Index to Educational Videotapes* (6th ed., 1985). If you know of additional films or videotapes in genetics, please let us know.

FILMS AND VIDEOTAPES

Agitans to Zig Zag
Allelism and Lethals
Antenatal Diagnosis for the Detection of Genetic Diseases
Approaches to Floppy Babies and Weak Children, and Genetic Counseling
The Ascent of Man: 12—Generation upon Generation
Assault on Life
Bacterial Genetics: Clones
Bacterial Genetics: Genetic Transduction
Bacterial Genetics: Sexual Reproduction
The Baby Makers
Basic Genetics
The Basic Nature of Sexual Reproduction
A Beautiful Baby Boy, But . . .
The Beginnings
Bicentennial of Medicine in the United States, 1776–1976—Human Genetics
Biochemical Approach to Evolution Divergence in a Species of Marine Snail
Biochemical Genetics
Biochemical Genetics I
Biochemical Genetics II
Biochemical Origin of Terrestrial Life
The Biological Sciences: Genetic Biology
Bionics
Black Male With Sudden Anemia, The G-6-PD Problem
Blood Groups, Skin Color, and Gene Pools
Blueprint for Life
The Born Criminal
Boy or Girl—Should the Choice be Ours?
Breeding Better Corn
Catch Your Mutant
The Cell, A Functioning Structure, Part III
Changes in Genome Number

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[1] From the Symposium on *Science as a Way of Knowing—Genetics* presented at the Annual Meeting of the American Society of Zoologists, 27–30 December 1985, at Baltimore, Maryland.

Chromatin
Chromosomal Abnormalities—Autosomes
Chromosomal Abnormalities—Sex Chromosomes
Chromosome Addition and Subtraction
Chromosome Banding Techniques
Chromosome Chemistry and Genetic Activity
Chromosome Classification and Purification by Flow Cytometry and Sorting
Chromosomes and Sex
Chromosomes: General Considerations
The Chromosomes of Man
A Clone of Frogs
The Code of Life
Color Her Sunshine
The Coming of the Clone
Cracking the Code of Life
Crossing Over, Chiasmata, and Genetic Maps
Crossing Over in Terms of Meiosis
Cytogenetics of Oenothera
Cytoplasm and Differentiation
Cytoplasmic Heredity
Development and Differentiation
Development of the Axolotl
Developmental Genetics I
Developmental Genetics II
Diagnosis of Hidden Congenital Anomalies
The Differences Are Inherited
Differential Gene Expression
DNA
DNA—Blueprint of Life
DNA—Key to Life
DNA and Genes
DNA—Molecule of Heredity
DNA and RNA—Deciphering the Code of Life
DNA—The Thread of Life
The DNA Story
DNA Structure and Replication
Elementary Genetics
Enzyme Defects and DNA
Evolution and the Origin of Life
Evolution by DNA: Changing the Blueprint of Life
The Evolution of Living Things (10): How Animals Change
Expression and Interaction of Genes
Extending Life Science
The Fabric of Life
Fact or Fallacy
The Fight to be Male
From Cells to Living Organisms
The Fruit Fly: A Look at Behavior Biology
The Future of the Species
Gene Action
The Gene Engineers
General Genetics—A Series
Genes of the Circle Line
Gene Structure and Gene Action
Genes and Chromosomes
Genes and Chromosomes in Mitosis and Meiosis (Revised Edition)
Genes and Development—A Series
Genes and Protein Synthesis
Genesis: The Origins of Human Life
Genesis 1, 27—Undersea World
Genetic Activity and Chromosome Activity
Genetic Biology
Genetic Chance
Genetic Counseling I—Heredity and Birth Defects
Genetic Defects: The Broken Code
Genetic Engineering
Genetic Fix
Genetic Investigations
Genetic Loads in Mendelian Populations
Genetic Manipulation of Wheat
Genetic Polymorphisms and Evolution
Genetic Revolution
Genetic Screening—The Ultimate in Preventive Medicine
Genetics
Genetics and Behavior
Genetics and Medicine
Genetics and Plant Breeding
Genetics and Recombinant DNA
Genetics in Childhood Malignancy
Genetics: Chromosomes and Genes—Meiosis
Genetics: Functions of DNA and RNA
Genetics: Human Heredity
Genetics: Improving Plants and Animals
Genetics: Man the Creator
Genetics: Mendel's Laws
Genetics: Observing Patterns of Inheritance
Genetics: The Genius of Mendel
Genetics of Mendelian Populations
The Genetics of Race
Genetics of Transplantation
Genetics: Parts 1 and 2

Genetics: Techniques of Handling Drosophila
Great Scientists Speak Again: Gregor Mendel
The Great Wine Revolution: Parts 1 and 2
Gregor Mendel
Handling and Sexing Fruit Flies
Heredity and Adaptive Change: The Chromosomes of Man
Heredity and Birth Defects
Heredity: Basis of Evolution
Heredity
Heredity and Environment
Heredity and the Chromosomes
Heredity and Variation
Heredity in Animals: Better Breeds
Heterosis
History of Genetics—Physical Basis of Inheritance
How to Build a Phage
Human Chromosomes and How They Are Studied
Human Gene Mapping by Somatic Cell Hybridization Techniques
Human Diversity
Human Genetics—A Series
Human Heredity
Human Traits Showing Simple Mendelian Inheritance
Immune Response Genes—Structure and Function
Improving Strains of Livestock
Inbreeding and Heterosis
Individual Differences: Infancy to Early Childhood
Inheritance in Man
Inheritance in Populations
Interactions in Heredity and Environment
Interspecific Hybridization and Its Consequences
Introduction to Drosophila Genetics
In Search of the Secrets of Life
It Runs in the Family
Invasion of the Virions
Laws of Heredity
Life Cycle
Life on Other Planets
The Life Cycle of a Flowering Plant, Part 1: The Plant Cell—Male and Female Flower Parts
The Life Cycle of a Flowering Plant, Part 2: Meiosis
The Life Cycle of a Flowering Plant, Part 3: Egg Cell Development—Mitosis
Life: Patent Pending
Linkage
Linkage—Population Genetics
The Living Cell: DNA
Living With Cystic Fibrosis
Macromolecular Biosynthesis
Many Pairs of Genes
Mechanism of Inheritance
Medical Genetics (Parts 1 and 2)
Medical Genetics (Part 3)
Meiosis
Mendel: Father of Genetics
Mendel's Experiments
Mendel's Proof of the Existence of Genes
Mendel's Recombination
Mendel's Recombination of Traits
Mendel's Segregation
Mendel's Segregation of Traits
Mitosis
Mitosis and Meiosis
Mitosis in Endosperm
Modifications Morphologiques du Canard Pekin par Injection d'Acide Desoxyribonucleique (ADN)
Molecular Evolution
Mr. Decathlon
Multiple Factor Inheritance
Musical Genes
Mutagen-Induced Gene Mutation
Mutation
Mystery of Life (The 21st Century Series)
Natural Selection: Evolution at Work
The Nature of Human Color Change—Genetic, Hormonal and Neoplastic
Nature and Nurture
Nature's Laws
A New Double Helical Model for DNA
Neurospora Techniques
Nuclear Radiation Fallout
Nuclear Transplantation
Nucleo-Cytoplasmic Relations in Paramecium
Numerical Abnormalities of Human Chromosomes
Obstetrics and Gynecology—A Series
On the Border of Life
One Voice in the Cosmic Fugue
Origins of Man
The Origin of Species
Parents Look at Genetic Counseling
Past, Present and Future

Pedigree Patterns—Medical Genetics
The Persistence of Memory
Plant Growth and Mutation in Tradescantia virginica L. (Spiderwort)
Picking the Winner
The Picture of Health—Genetic Platforms
Pleiotropism, Penetrance, and Expressivity
The Politics of Genetics
Polymorphism in Snails
Pre-Natal Diagnosis by Amniocentesis
Pseudoallelism
A Question of Values
Radiation and the Population
Recent Advances in Reproductive Morphology
Reproduction and Heredity
Research into Genetics
The Return of the Sky
RH—The Disease and its Conquest
RH-Negative Mother
Riddle of Heredity
The RII System
The Science of Genetics
Selection, Genetic Death and Genetic Radiation Damage
The Sex Chromosomes
Sex Determination I
Sex Determination II
Sex-linked Inheritance
Sexuality and Variation
Sickle Cell . . . An Inherited Disease
The Sickle Cell Story
Small Tumor Virus and the New Genetics
Sociobiology: The Human Animal
Species: Stability and Change
Spontaneous Gene Mutation
Stop or Go: An Experiment in Genetics
Structural Abnormalities of Human Autosomes
Structural Changes in Chromosomes, Part I
Structural Changes in Chromosomes, Part II
Study of Twins, Parts 1–4
The Stuff of Life
The Thread of Life
Threads of Life
The Treasury of Human Genes
Through the Genetic Maze—A Series
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Tree Improvement and Genetics
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Variations in Replication
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Virus Genetics: Plant and Animal Viruses
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